Clinical and angiographic predictors of outcome after primary angioplasty

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Chapter 1

General introduction

Cardio-vascular disease and complications are the main cause of death in the western world[1]. For many years therapy for acute myocardial infarction was restricted to treatment of complications, resulting in mortality rates of 15-20%. In 1980, De Wood showed that the cause of acute myocardial infarction is usually an intracoronary thrombotic occlusion, formed on a ruptured atherosclerotic plaque[2,3]. This opened a new approach for the therapeutic strategy of acute myocardial infarction, aimed on myocardial salvage by the timely restoration of coronary perfusion.

At first attention was focused on medical reperfusion therapies with intracoronary and intravenous thrombolytic agents. Furthermore the beneficial role of acetylsalicylacid and heparin became clear. These strategies reduced early mortality rates after acute myocardial infarction with 20-30%[4-11]. Although this was a significant step forward, the beneficial effect of thrombolytic therapy was limited by several factors. The reperfusion rates were modest[12] and accompanied by a risk of major bleeding complications[13], significant residual stenoses of the infarct related vessel in the majority of patients and a relatively high risk of reocclusion and thus re-infarction[7,8,14-22].

This initiated trials to assess the role of mechanical reperfusion by percutaneous coronary intervention (PCI). The advantage of primary PCI over thrombolytic therapy became clear after the first randomized trials. Higher patency rates, lower early and late mortality, a lower rate of additional revascularisation procedures and re-infarction and avoidance of intracerebral bleeding complications[23-26]. Additional therapies before, during and after the primary PCI, like effective platelet inhibition with glycoprotein IIb-IIIa antagonists[27], distal protection devices[28], mechanical and medical strategies to reduce reperfusion damage[29,30] and stem-cell therapies[31] have improved or may improve clinical outcome further. The major limitation of primary PCI is the availability. Primary coronary intervention is still only available in a limited number of hospitals. Therefore transportation to a PCI centre is often necessary with loss of valuable time and thus of muscle, resulting in impaired prognosis[32,33].

Contents of this thesis.

In this thesis we address the impact of several clinical and angiographic aspects on clinical outcome in a setting where patients presenting with acute MI are systematically treated with early primary PCI.

In the second chapter the role of anginal complaints, in the hours and days before the acute coronary occlusion, is addressed. We tried to clarify whether pre-infarction angina delays myocardial necrosis by ischaemic preconditioning or by induction of collateral flow.

In the third chapter we have tried to determine at what time post-infarction the calculated amount of cumulative Lactate Dehydrogenase becomes representative for the total amount of myocardial cell loss, in an attempt to identify an early biomarker for prognosis.

The fourth chapter is based on the fact that over a period of weeks to months, collateral flow will be recruited to the area of a chronic coronary occlusion. In how many patients these collaterals are already present in the first hours of the acute coronary occlusion and whether collateral flow may have a preserving effect on the myocardium at risk in the setting of early primary PCI is studied in this chapter.

The fifth chapter is focused on the question whether the worse prognosis of LAD related infarcts is solely due to the larger infarct size, or whether other aspects of anterior infarct location play a role. Therefore we compared LVef, adjusted for enzymatic infarct size, to evaluate whether a given amount of cell necrosis affect LVef the same in different infarct territories.

The sixth chapter is focused on the question whether the infarct location related risk stratification in acute MI patients, as defined in patients treated with thrombolysis, is still relevant in patients treated with primary PCI. Therefore we compared proximal and distal coronary occlusion sites of the three coronary arterial beds for infarct size and prognosis.

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Chapter 2

Clinical characteristics and outcome of patients with acute myocardial infarction and pre-infarction angina

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Abstract

OBJECTIVES/BACKGROUND: Preinfarction angina is associated with reduced myocardial infarct size in patients treated with thrombolysis. Our objective was to assess the relation between preinfarction angina and infarct size, left ventricular function and clinical outcome in patients treated with primary angioplasty (PTCA) and compare this with patients treated with thrombolysis.

METHODS: In the Zwolle Infarction Study 982 patients were treated for acute myocardial infarction between 1990 and 1996. In 29 patients the history of antecedent angina was not available. Included were 953 patients, 761 patients underwent primary PTCA and 192 patients received thrombolysis as reperfusion therapy.

RESULTS: Preinfarction angina was present in about 50% of the patients, categorised in ≤ 24 hours and > 24 hours before infarction. In patients in both treatment groups, ischemic time is longer when preinfarction angina is present. In patients treated with thrombolysis, preinfarction angina ≤ 24 hours results in a smaller enzymatic infarct. Thrombolysis seems to be more effective when preinfarction angina occurs ≤ 24 hours. Collateral filling of the infarct related artery is more often seen in patients with preinfarction angina. In the primary PTCA group a longer ischemic time in patients with preinfarction angina does not result in increased infarct size, and this effect remains after excluding patients with collateral filling.

CONCLUSIONS: The protective effect of preinfarction angina is likely due to better collateral filling of the infarct related artery and to ischemic preconditioning of the myocardium.

Introduction

In many patients brief episodes of angina precede acute myocardial infarction. Experimental and clinical studies have shown that episodes of angina in the hours before sustained coronary occlusion are associated with reduced myocardial infarct size and better preserved left ventricular function[1-14]. Until now mechanisms and clinical significance are not clear. In some clinical studies brief episodes of ischemia alternated with reperfusion in the first 24 hours before infarction result in preconditioning of the myocardium and make it more resistant to injury resulting from a subsequent longer ischemic episode[1-8]. Other mechanisms that may play a role are more rapid reperfusion after thrombolysis in patients with pre-infarction angina[13] or differences in the development of collateral flow[11]. Until now, most clinical studies that showed a protective effect of pre-infarction angina on infarct size and left ventricular function have been done in patients treated with thrombolysis. This therapy accomplishes reperfusion in about 60-80% of patients. Without acute coronary angiography it is not possible to investigate whether the protective effect of pre-infarction angina is due to earlier reperfusion, preconditioning or collateral blood flow. Recent data from a large myocardial infarction registry showed no protective effects of pre-infarction angina in patients with acute myocardial infarction treated with primary angioplasty (PTCA)[15].

Therefore, we thought to study the relation between pre-infarction angina and infarct size, left ventricular function and clinical outcome in patients treated with primary PTCA and to compare this with patients treated with thrombolysis. In the patients treated with primary PTCA the time of reperfusion during angiography and angioplasty is known, and that allows us to investigate which mechanism would most likely be involved in a beneficial effect of pre-infarction angina.

Methods

Between August 1990 and December 1996, 982 patients with acute myocardial infarction were enrolled in the Zwolle Infarction Study. Details regarding inclusion and exclusion criteria have been published[16-17]. Selection of reperfusion therapy (thrombolysis or angioplasty) was performed by randomization. Inclusion criteria were symptoms of acute myocardial infarction that persisted for more than 30 minutes, with more than 1 mm (0,1mV) ST segment elevation in two or more contiguous electrocardiographic leads. A detailed history of antecedent angina was taken at admission. Infarct size was measured by calculation of cumulative lactate dehydrogenase (LDH) release up to 72 hours after symptom onset. Samples were obtained on admission and every 12 hours up to 72 hours. From these measurements, an area under the curve was calculated, preferably from 7, but at least from 5 measurements. These measurements and calculations were performed at the department of clinical chemistry, without access to the clinical data. Streptokinase was used as the thrombolytic drug in a dose of 1.5 million units intravenously over a period of one hour. Left-ventricular ejection fraction was measured with a radionuclide technique, as described earlier[16]. Patients with pre-infarction angina were categorised with regard to the time between onset of angina and myocardial infarction in three groups namely: 1. ≤24 hours, 2. > 24hours or 3. no angina. Ischemic time was defined as time between onset of symptoms and first balloon inflation or start of thrombolysis. In the primary PTCA treatment group coronary angiography was performed as quickly as possible. Arterial patency was defined as Thrombolysis in Myocardial Infarction (TIMI) grade 2 or 3 flow of the infarct related artery [18]. When at first contrast injection of the infarct related artery TIMI 0 or 1 flow was seen, the collateral filling from the patent vessels was graded according to the Rentrop criteria[19]. In the thrombolysis patients an elective coronary angiography was performed following the initial conservative approach[20].

Statistical analysis

The GB-STAT: V6.5 program was used for data analysis. In our presentation of the data, continuous baseline and outcome are given as means ± SD, whereas discrete variables are given as absolute values and percentages. Continuous variables were compared by the students t-test. Independent variables were compared by Mann-Whitney U test. Differences were considered significant at $p< 0.05$.

Table 1. characteristics of patients treated with primary PTCA

	Preinfarction angina			No angina
	≤24h	>24h	all	
	n=144	n=232	n=376	n=385
Age, year	60	60	60	59
Male, n(%)	110(76)	186(80)	296(79)	315(82)
Hypertension, n(%)	26(18)	54(23)	80(21)	68(18)
Diabetes, n(%)	14(10)	20(9)	34(9)	24(6)
Family history CAD, n(%)	59(41)	103(44)	162(43)	149(39)
Smoker, n(%)	68(47)	111(48)	179(48)	172(45)
Prior MI, n(%)	16(11)	37(16)	53(14)	55(14)
Prior PTCA, n(%)	14(10)	17(7)	31(8)	20(5)
Prior CABG, n(%)	7(5)	7)3)	14)4)	6(2)
IRV: n(%)				
LAD	74(51)	114(49)	188(50)	203(53)
CX	23(16)	29(13)	52(14)	47(12)
RCA	44(31)	82(35)	126(34)	129(34)
Graft	2(1)	2(1)	4(1)	3(1)
VD: n(%)				
1	63(44)	82(35)*	145(39)‡	176(46)
2	43(30)	72(31)	115(31)	112(29)
3	38(26)	78(34)†	116(31)	97(25)
TIMI before PTCA				
0	97(67)	161(69)	258(69)	259(67)
1	20(14)	28(12)	48(13)	37(10)
2	10(7)	25(11)	35(9)	35(9)
3	15(10)	17(7)	32(9)	36(9)
TIMI after PTCA				
0	3(2)	8(3)	11(3)	11(3)
1	1(1)	4(2)	5(1)	10(3)
2	9(6)	14(6)	23(6)	25(6)
3	130(90)	206)89)	336(89)	332(86)
Collateral flow	97(67)	157(68)	254(68)	272(71)
0	61(62)	102(65)	163(65)	195(72)
1	28(29)	47(30)	75(30)	64(24)
2	7(7)	0	7(3)	11(4)
3	1(1)	8(5)	9(4)	2(1)

*p=0.01, †p=0.03, ‡p=0.04

Table 2. Characteristics of patients treated with thrombolysis.

	Preinfarction angina			No angina
	≤24h	>24h	all	
	n=39	n=57	n=96	n=96
Age, year	62	59	60	60
Male, n(%)	32(82)	47(82)	79(82)	73(76)
Hypertension, n(%)	7(18)	14(25)	21(22)	15(16)
Diabetes, n(%)	3(8)	4(7)	7(7)	5(5)
Family history CAD, n(%)	15(38)	23(40)	38(40)	35(36)
Smoker, n(%)	22(56)	31(54)	53(55)	47(49)
Prior MI, n(%)	4(11)	12(21	16(17)	16(17)
Prior PTCA, n(%)	2(5)	5(9)	7(7)	4(4)
Prior CABG, n(%)	3(8)	4(7)	7(7)	8(8)
IRV: n(%)				
LAD	14(36)	15(26)	29(30)	28(30)
CX	5(13)	7(12)	12(13)	14(15)
RCA	13(33)	21(37)	34(35)	39(41)
Graft	0	2(4)	2(2)	2(2)
VD: n(%)				
1	15(38)	27(47)	142(44)	47(49)
2	8(21)	12(21)	20(21)	24(25)
3	14(36)	17(30)	31(32)	21(22)

Results

Between August 1990 and December 1996, 982 patients were enrolled in the Zwolle Infarction Study. The history of antecedent angina was not available in 29 patients (20 patients in the primary PTCA group and 9 patients in the thrombolysis group). So analysis was performed on 953 patients; 761 treated with primary PTCA and 192 with thrombolysis. Pre-infarction angina was reported by 376 patients (144 < 24h and 232 > 24h) in the primary PTCA treated group and 96 (39 < 24h and 57 > 24h) in the thrombolysis treated group. Table 1 and 2 show the baseline characteristics of the patients. In the primary PTCA group, the incidence of 3 vessel disease was higher in patients with pre-infarction angina > 24h. In the thrombolysis treated group baseline characteristics showed no differences. Table 3 shows the comparison of

ischemic time, enzymatic infarct size, radio-nuclide left ventricular ejection fraction and collateral flow, in relation to time between onset of angina and infarction. Left ventricular ejection fraction was measured in 864 (91%) patients and cumulative LDHQ72 in 844 (89%) patients. In both treatment groups, pre-infarction angina is associated with a longer ischemic time. Enzymatic infarct size is comparable. In 13% of the angiograms with TIMI flow 0 or 1, collateral flow could not be graded for technical reasons. Collateral filling was more often seen in patients with pre-infarction angina. In the thrombolysis group episodes of angina within 24 hours before myocardial infarction are associated with a smaller enzymatic infarct size, compared with patients without pre-infarction angina, and with a shorter ischemic time. A tend to a higher rate of combined previous events (MI, PTCA, CABG) (37% vs 23% and 29% p=ns) may play a confounding role. Table 4 shows the cardiac event rates at 1 year follow-up in relation to timing of pre-infarction angina. In the primary PTCA group, patients with pre-infarction angina > 24 hours died more of a cardiac cause which may be related to the higher rate of 3 vessel disease in this group.

Table 3. Ischaemic time and infarct size.

Primary PTCA	Preinfarction angina			No angina
	≤24h	>24h	all	
	n=144	n=232	n=376	n=385
Ischaemic time (min)	293±236*	265±184†	276±207‡	233±163
LDHQ72 (U/l)	1097±879	1257±1092	1193±1017	1222±911
LVef (%)	44±11	46±12	46±11	44±11

*p=0.04, †p=0.003, ‡p=0.002

Thrombolysis	Preinfarction angina			No angina
	≤24h	>24h	all	
	n=39	n=57	n=96	n=96
Ischaemic time (min)	185±110	326±311*	266±258‡	167±110
LDHQ72 (U/l)	957±750‡	1383±1374	1201±1175	1429±1116
LVef (%)	46±11	42±11	44±11	45±11

*p=0.003, †p=0.004, ‡p=0.03

Tables 3a. Pre-PTCA TIMI1 or 0 flow: collaterals, ischaemic time and infarct size.

Primary PTCA		Preinfarction angina		No angina
	≤24h	>24h	all	
	n=117	n=189	n=306	n=296
Ischaemic time (min)	293±231*	265±190†	276±207‡	239±178
LDHQ72 (U/l)	1168±908	1367±1128	1287±1048	1304±914
LVef (%)	45±11	46±11	46±11	44±12
Collaterals (%)	37§	35	36¶	28

*p=0.05, †p=0.02, ‡p=0.007, § p=0.06, ¶p=0.04

Tables 3b. Pre-PTCA TIMI1 or 0 flow without collaterals: ischaemic time and infarct size.

Primary PTCA		Preinfarction angina		No angina
	≤24h	>24h	all	
	n=61	n=102	n=163	n=195
Ischaemic time (min)	274±200	265±188*	268±192*	234±162
LDHQ72 (U/l)	1182±1001*	1327±1119	1270±1073	1345±918
LVef (%)	45±10	46±12†	46±11‡	43±11

*p=0.09, †p=0.008, ‡p=0.01

Discussion

This study shows that patients with pre-infarction angina wait longer to seek medical attention when having persisting anginal complaints suggestive for acute myocardial infarction, leading to a longer coronary occlusion time. Though, otherwise as expected, enzymatic infarct size is comparable, as is the left ventricular ejection fraction. Thrombolysis seems to be more effective in patients that have had episodes of angina within 24 hours before myocardial infarction when compared to patients with angina > 24 hours or without preinfarction angina.

Pre-infarction angina seems to protect the myocardium after sustained coronary occlusion.

Mechanisms which may play a role are 1.Coronary collateral flow, 2.Faster reperfusion and 3.Ischemic preconditioning.

Table 4. Events at 1 year.

Primary PTCA	Preinfarction angina			No angina
	≤24h	>24h	all	
	n=144	n=232	n=376	n=385
Recurrent MI	6(4)	6(3)	12(3)	15(4)
Recurrent PTCA	26(18)	37(16)	63(17)	62(16)
CABG	23(16)	40(17)	63(17)	46(12)
Death all causes				
4 weeks	8(6)	13(6)	21(6)	14(4)
1 year	9(6)	19(8)	28(7)	22(6)
Death cardiac causes				
4 weeks	7(5)	12(5)	19(5)	13(3)
1 year	7(5)	18(8)*	25(7)†	14(4)

*p=0.04, †p=0.06

Thrombolysis	Preinfarction angina			No angina
	≤24h	>24h	all	
	n=39	n=57	n=96	n=96
Recurrent MI	6(15)	11(19)	17(18)	19(18)
Recurrent PTCA	16(41)	28(49)	44(46)	51(53)
CABG	9(23)	11(19)	20(21)	15(16)
Death all causes				
4 weeks	1(3)	3(5)	4(4)	6(6)
1 year	1(3)	3(5)	5(5)	10(10)
Death cardiac causes				
4 weeks	2(5)	2(4)	3(3)	5(5)
1 year	2(5)	2(4)	4(4)	7(7)

Coronary collateral flow.

In the primary PTCA group collateral filling of the infarct related artery by the patent arteries is more often present in patients with pre-infarction angina.

Reperfusion rate

The mechanisms of reperfusion by primary PTCA or thrombolysis are fundamentally different. Thrombolysis is a pharmacologic reperfusion therapy and is less successful in restoring patency than primary PTCA[16-17]. The resistance of coronary artery occlusion to thrombolysis may be due to obstruction of the lumen by a mechanical nonthrombotic mechanism or by intrinsic resistance of thrombus to dissolution.

Primary PTCA restores perfusion by mechanical means and success is less dependent on the cause and duration of the occlusion. In our primary PTCA group no differences were seen in reperfusion success. In patients having angina within 24 hours before myocardial infarction, thrombolysis seems to be more effective. A higher percentage of the ischemic episodes < 24 hours before infarction might be due to unstable lesions. Platelet-rich arterial thrombi are much more resistant to thrombolysis than erythrocyte-rich thrombi[21]. The thrombus formed at the plaque fissure is very rich in platelets, whereas proximal and distal extension of the thrombus are composed of erythrocyte rich material[22]. Occluding thrombi on stable or unstable lesions might differ in platelet/erythrocyte composition, which could be an explanation for the differences in effectivety of thrombolysis. In primary PTCA the morfology and age of the occluding thrombus seems not to influence the effectiveness of reperfusion. Another explanation could be related to differences in the mechanical component of the obstruction that may be more amenable by angioplasty compared to a pharmacological approach.

Ischemic preconditioning.

A protective effect of pre-infarction angina can still be observed after exclusion of patients with collateral filling of the infarct related artery. Since in primary PTCA no differences in reperfusion rate were present, preconditioning must also play a role.

A limitation of this study is that collateral flow is determined by angiography, which is able to detect epicardial collaterals but the presence of small intramural or microvascular collaterals can not be excluded. In our analysis only symptomatic episodes of pre-infarction ischemia are determined, so possible episodes of silent ischemia, which may also play a role in preconditioning of the myocardium, are not taken into consideration. Although enzymatic infarct size is comparable in the primary PTCA group we may presume that pre-infarction angina protects the jeopardised myocardium since the extend of myocardial cell death is related to ischemic time.

In conclusion our study confirms the differences in the effect of pre-infarction angina in patients treated with primary PTCA versus thrombolysis[15]. Thrombolysis is more efficient in patients with ischemic episodes within 24 hours before myocardial infarction. This could be helpful in selecting a group of patients, which benefit most of thrombolysis. The results in primary PTCA suggests a protective effect of both angina ≤ 24 hours as well as angina > 24 hours before myocardial infarction. Pre-infarction angina is associated with more collateral filling of the infarct related artery, which could play a role in the protective effect, although a protective effect is also present in patients without collaterals, which supports the hypothesis of protection due to preconditioning[4-10].

Both collateral filling as well as ischemic preconditioning has a protective effect in patients with pre-infarction angina. In our analyses pre-infarction angina is also associated with longer ischemic time, due to longer patient delay[15]. So the clinical benefits of the protective effect of pre-infarction angina may be increased by better patient instruction in seeking medical attention when anginal complaints persist at rest for more than 30 minutes.

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Chapter 3

The predictive value of cumulative Lactate Dehydrogenase release within the first 72 hours of acute myocardial infarction in patients treated with primary angioplasty

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Abstract

Background: In patients with acute myocardial infarction, estimation of infarct size by cumulative Lactate Dehydrogenase release at 72 hours ($LDHQ_{72}$) is a simple and widely used method. Our objective was to study the value of estimating infarct size, by the cumulative release of LDH over 72, 60, 48 and 36 hours respectively, in predicting left ventricular ejection fraction (LVef) and cardiac death at 1 year.

Methods: In the Zwolle Infarction Study infarct size estimated as LDHQ was calculated in 1224 patients treated with primary percutaneous coronary intervention (PCI) for acute myocardial infarction between December 1993 and June 2001. Patients were categorized as having small ($LDHQ_{72}$ < 800 U/l), medium ($LDHQ_{72}$ 800-2500 U/l) or large ($LDHQ_{72}$ > 2500 U/l) myocardial infarction.

Results: $LDHQ_{72}$ was closely correlated with $LDHQ_{60}$, $_{48}$ and $_{36}$ (r=0.998, 0.993 and 0.987 respectively $p < 0.0001$). The relations between LDHQ infarct size classification and mean LVef (51% vs 45% vs 35% $p<0.0001$) or 1 year cardiac death (0-0.3% vs 0.7-1% vs 6-8%) showed a similar pattern, irrespective of whether LDH was measured up to 36, 48, 60 or 72 hours.

Conclusions: Infarct size classification based on $LDHQ_{36}$ is an objective and widely available method for early risk stratification in patients treated with primary angioplasty for acute ST-segment elevation myocardial infarction.

Introduction

In patients with acute myocardial infarction, estimation of enzymatic infarct size can be used to investigate the efficacy of reperfusion therapy and to predict clinical outcome[1-3]. In large reperfusion trials different models have been used. Enzymatic infarct size has been estimated by measurement of peak Creatine Kinase (CK) or CK area under the curve[4-5] and by measurement of cumulative Lactate Dehydrogenase release up to 72 hours ($LDHQ_{72}$)[1,2,6,7]. Other cardiac markers like myoglobin and fatty acid binding protein are released within 24 hours, but suffer from the effects of impaired renal function producing a gross overestimation of infarct size in 25% of patients[8]. Following successful reperfusion, cardiac enzymes will be released over a shorter time period[1,9]. Compared with an identical amount of myocardial damage, early reperfusion leads to an earlier CK peak and to higher maximum CK-levels, which leads to overestimation of infarct size[10-12]. CK is rapidly catabolized and there is a 20% between patient variation in fractional catabolic rates. The individual variation in fractional catabolic rate is unknown[13]. LDH is eliminated more slowly, so a greater proportion of the activity released from the infarcted myocardium remains in the circulation. LDH release may continue for 96 hours post infarct though for practical reasons the $LDHQ_{72}$ is used to determine infarct size, since $LDHQ_{72}$ is equal to ≥ 95% of $LDHQ_{96}$ (14). The cumulative LDH release has a better correlation to left ventricular ejection fraction than peak-CK and CK area under the curve[15]. Therefore, estimation of the $LDHQ_{72}$ is up till now the preferable marker enzyme for estimating infarct size, assessment of reperfusion effectiveness and prediction of clinical outcome.

These data are mainly from trials with thrombolysis as reperfusion therapy, which has a success rate of 60-80%. In these studies enzymatic infarct size is determined in a heterogeneous group of patients, with and without reperfusion, and thus with different dynamics of enzyme release. By primary percutaneous coronary intervention (PCI) reperfusion is accomplished in more than 90% of patients with acute ST-elevation myocardial infarction and the time of reperfusion

is known. This gives us the opportunity to determine enzymatic infarct size in a more homogeneous group of patients. Recent studies show that for an extensive group of patients, presenting with acute myocardial infarction at hospitals without PCI capacity, transfer for primary angioplasty is the best reperfusion therapy[16,17]. In our experience these patients are transferred back to the hospital of presentation within 24-48 hours post-intervention. Early risk stratification, available before transferring to the presenting hospital, could be a guide to optimize post-intervention reactivation, monitoring and treatment. In all patients with coronary artery disease left ventricular function is a strong predictor of survival [18-22]. Though not all hospitals have the possibility to determine left ventricular function by angiography, radionuclide technique or echocardiography in the first post-infarction days, almost all hospitals have a clinical chemistry laboratory. Therefore, we studied the value of enzymatic infarct size, estimated as $LDHQ_{72}$, in predicting left ventricular ejection fraction (LVef) and cardiac death at 1 year. We compared this predictive value with the cumulative LDH release calculated at 60, 48 and 36 hours, to determine whether $LDHQ_{36}$ could be used as a widely available, early risk stratification by representing myocardial damage and predicting clinical outcome and LVef, in patients presenting with ST-segment elevation myocardial infarction.

Table 1a. Baseline characteristics LDHQ72

	<800 (U/l) n=103	800-2500 (U/l) n=211	>2500 (U/l) n=131
Age (year)	59±10	59±11	59±12
Male, n(%)	81(79)	170(81)	102(78)
Ischemic time (min)	192±73	189±63	196±65
Previous PCI, n(%)	7(7)	7(3)	2(2)
Previous CABG, n(%)	0	2(1)	2(2)
Hypertension, n(%)	25(24)	42(20)	29(22)
Diabetes mellitus, n(%)	12(12)	18(9)	10(8)
Current smokers, n(%)	45(44)	101(48)	62(47)
Hypercholesterolaemia, n(%)	21(20)	32(15)	15(11)
Family history, n(%)	36(35)	77(36)	51(39)
Anterior infarction, n(%)	44(43)	96(45)	87(66)*
Multi-vessel disease, n(%)	50(49)	100(47)	69(53)
Successful PCI, n(%)	95(96)	205(98)	125(96)

*p<0.001

PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting
Hypertension was defined as > 150/90 mmHg on 3 occasions
Hypercholesterolaemia was defined as ≥ 6,5 mmol/l

Table 1b. Baseline characteristics LDHQ60

	<800 (U/l) n=189	800-2500 (U/l) n=332	>2500 (U/l) n=210
Age (year)	60±11	59±11	59±12
Male, n(%)	144(76)	266 (80)	173 (82)
Ischemic time (min)	188±75	191±63	195±68
Previous PCI, n(%)	9(5)	9(3)	6(3)
Previous CABG, n(%)	0	7(2)	2(1)
Hypertension, n(%)	48(25)	62(19)	46(22)
Diabetes mellitus, n(%)	16(8)	26(8)	13(6)
Current smokers, n(%)	88(47)	157(47)	107(51)
Hypercholesterolaemia, n(%)	32(17)	59(18)	24(11)
Family history, n(%)	70(37)	124(37)	76(36)
Anterior infarction, n(%)	82(43)	132(40)	145(69)*
Multi-vessel disease, n(%)	91(48)	162(49)	110(52)
Successful PCI, n(%)	180(97)	319(97)	202(97)

*p<0.0001

Table 1c. Baseline characteristics LDHQ48

	<800 (U/l) n=249	800-2500 (U/l) n=412	>2500 (U/l) n=239
Age (year)	60±12	59±11	59±11
Male, n(%)	191(77)	337(82)	190(78)
Ischemic time (min)	191±73	192±63	198±68
Previous PCI, n(%)	12(5)	10(2)	6(3)
Previous CABG, n(%)	2(1)	8(2)	3(1)
Hypertension, n(%)	67(27)	79(19)	57(24)
Diabetes mellitus, n(%)	21(8)	36(9)	15(6)
Current smokers, n(%)	121(49)	194(47)	124(52)
Hypercholesterolaemia, n(%)	49(20)	73(18)	33(14)
Family history, n(%)	100(40)	162(39)	87(36)
Anterior infarction, n(%)	104(42)	171(42)	167(70)*
Multi-vessel disease, n(%)	120(48)	204(50)	131(55)
Successful PCI, n(%)	241(98)	397(97)	230(97)

*p<0.0001

Table 1d. Baseline characteristics LDHQ36

	<800 (U/l) n=328	800-2500 (U/l) n=467	>2500 (U/l) n=232
Age (year)	60±11	59±11	58±11
Male, n(%)	257(78)	379(81)	184(79)
Ischemic time (min)	190±72	193±63	198±68
Previous PCI, n(%)	15(5)	9(2)	6(3)
Previous CABG, n(%)	4(1)	10(2)	1(0,4)
Hypertension, n(%)	82(25)	95(20)	57(25)
Diabetes mellitus, n(%)	26(8)	43(9)	16(7)
Current smokers, n(%)	153(47)	223(48)	126(54)
Hypercholesterolaemia, n(%)	67(20)	81(17)	31(13)
Family history, n(%)	128(39)	191(41)	82(35)
Anterior infarction, n(%)	135(41)	212(45)	167(72)*
Multi-vessel disease, n(%)	155(47)	232(50)	127(55)
Successful PCI, n(%)	319(98)	449(97)	224(97)

*p<0.0001

Methods

Patients

Between December 1993 and June 2001, 1224 patients with a first acute myocardial infarction with symptoms lasting < 6 hours were treated with PCI. Patients with LDHQ measured were enrolled in this study. Because we also wanted to determine the predictive value of the actual infarct size on LVef, we excluded patients with a previous myocardial infarction. Indications for PCI were symptoms of acute myocardial infarction that persisted for more than 30 minutes, with more than 1 mm (0,1 mV) ST segment elevation in two or more contiguous electrocardiographic leads. All patients received aspirin (500 mg intravenously), heparin (> 4000 IU intravenously) and nitroglycerin intravenously in a dose designed to maintain a systolic blood pressure of 110 mmHg. Baseline clinical characteristics and outcome data were collected in a case record form. Ischemic time is defined as time between onset of symptoms and first balloon inflation. LVef was measured with a radionuclide technique, as described earlier [21]. Coronary angiography and PCI of the infarct related artery were performed as quickly as possible. Arterial patency was determined as Thrombolysis in Myocardial Infarction (TIMI) grade 2 or 3 flow of the infarct related artery[23].

Blood sampling and biochemical assays

Blood samples were drawn on admission and after 3, 12, 24, 36, 48, 60 and 72 hours. LDH activity was determined enzymatically on a Hitachi 717 automatic analyzer according to the International Federation of Clinical Chemistry (IFCC) recommendation at 30°C[6]. Reference values for LDH are < 320 U/l (adults). Infarct size was estimated by measurements of enzyme activities using LDH as the reference enzyme. This method is equal to estimation of infarct size from α-hydroxybutyrate (HBDH) and has been described in detail[1,6]. Cumulative enzyme release was calculated at 36, 48, 60 and 72 hours at the department of clinical chemistry with blinding to all data other than hospital registration number and date of birth. A two-

compartment model was used, which has been validated in several studies on the turnover of ratio-labeled plasma proteins and the circulating tissue enzymes. The plasma activity c of the enzyme at time t is determined by release of the enzyme from the heart and elimination of the enzyme determined by a fractional catabolic rate constant (FCR_{LDH}). In addition, there is an extravasation of enzyme, determined by a fractional transcapillary escape rate constant (TER), and return to plasma from the extravascular return rate constant (ERR). Cumulative release of enzyme per liter of plasma from zero time up to time t is given by: $Q(t)=C(t)+E(t)+{}_0\int^t FCR_{LDH}.\ C(\tau)d\tau$ values of C(t) and E(t) are the activities still present in the intra vascular and extra vascular spaces. A value of $FCR_{LDH}=0.015\ h^{-1}$ was used. The extra vascular pool E(t) is determined by time-dependent plasma activity and TER and ERR:

$E(t)=TER.exp(-ERR.t).{}_0\int^t exp(ERR.\tau)C(\tau)d\tau$. Values of C(t) were obtained by subtraction of the normal activities in plasma from the actual activities measured at time t. Individual values of these normal activities were estimated from a sample taken from each patient when this sample was obtained within 3 hours after first symptoms. Otherwise, a fixed mean normal value of 175 U/l was used. Fixed values of TER=0,014 h^{-1} and EER=0,018 h^{-1} was used.

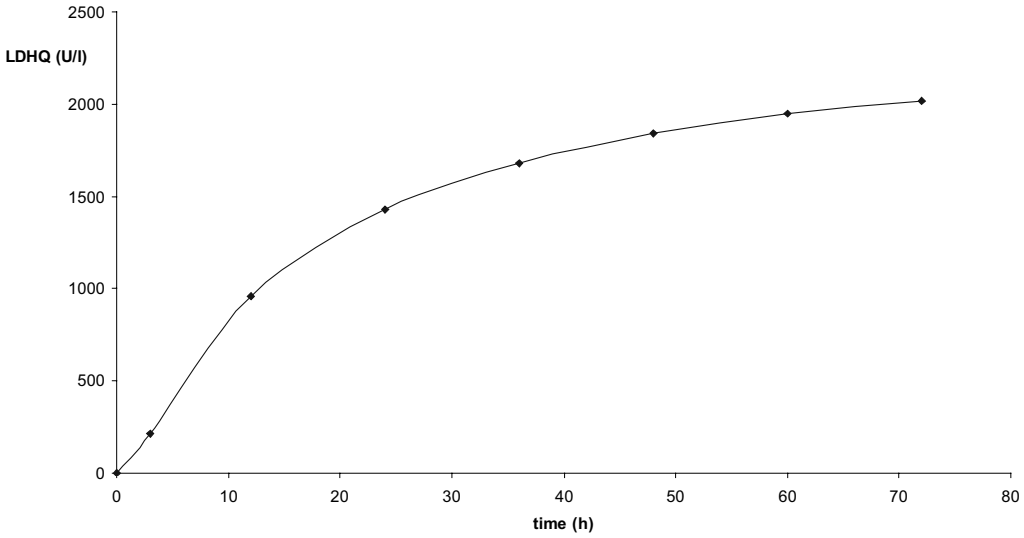

Figure 1. Cumulative lactate dehydrogenase release (LDHQ) in time after acute myocardial infarction treated with early percutaneous coronary intervention.

Data-analysis and statistics

With regard to clinical outcome and LVef, patients were divided in 3 groups representing small, medium and large infarction, defined as $LDHQ_{72}$ < 800 U/l, $LDHQ_{72}$ 800-2500 U/l and $LDHQ_{72}$ > 2500 U/l (24). We also estimated infarct size as cumulative LDH release at 60, 48 and 36 hours ($LDHQ_{60}$, $_{48}$ and $_{36}$) and used the same classification defining small, medium and large infarction as used in $LDHQ_{72}$ group.

Data are presented as means and standard deviations for continuous baseline and outcome, whereas discrete variables are given as absolute values and percentages. Differences between group means were assessed with the two-tailed Student's t-test. Mann-Whitney U test was used to test differences between proportions. Parametric, least square correlation was used for comparing LVef with LDHQ and orthogonale regression according to Passing and Bablok (25) was used for the comparison of $LDHQ_{36}$ with $LDHQ_{72}$ etc. Differences were considered significant at $p < 0.05$.

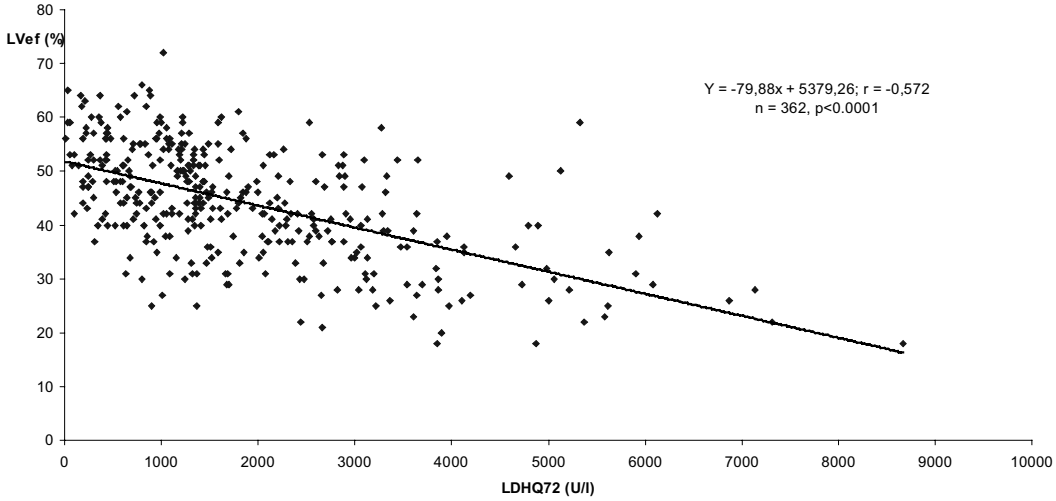

Figure 2A. Correlation between left ventricular ejection fraction (LVef) and cumulative lactate dehydrogenase release at 72 hours post infarct ($LDHQ_{72}$).

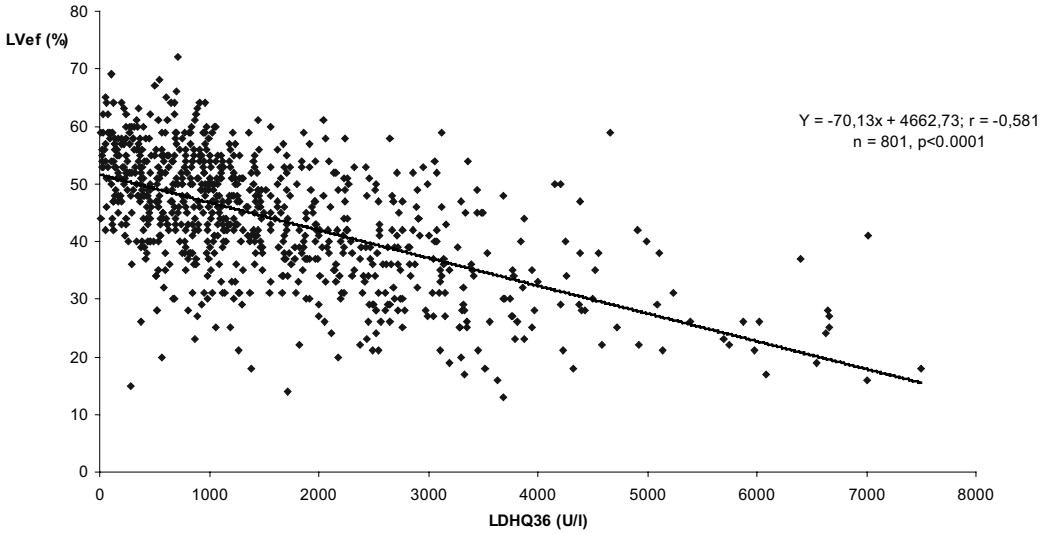

Figure 2B. Correlation between left ventricular ejection fraction (LVef) and cumulative lactate dehydrogenase release at 36 hours post infarct ($LDHQ_{36}$).

Results

LDHQ was calculated up to 72 hours in 445 patients, up to 60 hours in 731 patients, up to 48 hours in 900 patients and up to 36 hours in 1027 patients. One year follow-up was completed in 990 (96.4%) patients. Baseline characteristics are shown in table 1. There was a tendency for a lower rate of hypercholesterolaemia in patients with a large enzymatic infarct size. In the small infarct size group a trend was seen for a higher rate of previous PCI. Otherwise there are no differences in baseline clinical characteristics between $LDHQ_{72}$ versus $LDHQ_{60}$, $_{48}$ and $_{36}$. Ischemic time was similar in the three infarct size groups. In the patients with small (LDHQ < 800 U/l) and medium (LDHQ 800-2500 U/l) infarction the percentage of anterior infarction was similar, but the percentage of anterior infarction was higher in the large (LDHQ > 2500 U/l) infarction group ($p < 0.0001$). Between the three infarct size groups, PCI success rates were identical (97.5% ± 0.7, 97.1% ± 4, 96.8% ± 4). Figure 1 shows the relation between LDHQ and time after the onset of infarction. Eighty-three percent of the $LDHQ_{72}$ is already released at 36 hours after the onset of infarction. The correlation coefficients of $LDHQ_{72}$ with $LDHQ_{60}$, $LDHQ_{48}$ and $LDHQ_{36}$ were 0,998, 0,993 and 0,987 respectively ($P < 0,0001$ for all three comparisons). Table 2, shows mean LDHQ, LVef and death at 1 year follow-up for small, medium and large infarction size estimated as $LDHQ_{72}$, $LDHQ_{60}$, $LDHQ_{48}$ and $LDHQ_{36}$. LVef was measured in 70% of the patients. The relationship between LVef and LDHQ showed a similar pattern, irrespective of whether enzymes were measured over 36, 48, 60 or 72 hours. Patients with a small infarction had an almost normal LVef, medium enzymatic infarct size results in an slightly diminished LVef and a large enzymatic infarct size results in a poor LVef (51% vs 45% vs 35% $p < 0.0001$). At 1 year follow-up in the small infarction group, no cardiac death was seen in LDHQ calculated at 72, 60, and 48 hours and 1(0.3%) cardiac death in the $LDHQ_{36}$ group. In the medium sized infarction group 0.7-1% and in the large infarction group 6 to 8% died from a cardiac cause at 1 year (table 2). Figure 2.A shows a significant correlation between LVef and $LDHQ_{72}$ ($r=0.57$, $p < 0.001$). This correlation remains when enzymatic infarct size is estimated as $LDHQ_{36}$ ($r=0.58$, $p < 0.001$) as seen in figure 2.B.

Table 2. Enzymatic infarct size, left ventricular ejection fraction and death.

LDHQ72	<800 (U/l)	800-2500 (U/l)	>2500 (U/l)
	n=103	n=211	n=131
Mean LDHQ (U/l)	435	1474	4138
LVef (%)	51±7*	45±9*	36±10*
Death at 1 year, n(%): all cause	0	5(2,4)*	18(13,7)*
cardiac	0	3(1,4)*	16(12,2)*

*p<0.001

LDHQ60	<800 (U/l)	800-2500 (U/l)	>2500 (U/l)
	n=189	n=332	n=210
Mean LDHQ (U/l)	441	1469	4109
LVef (%)	51±8*	46±9*	35±10*
Death at 1 year, n(%): all cause	1(0,5)*	8(2,4)*	22(10,5)*
cardiac	0	5(1,5)*	20(9,5)*

*p<0.001

LDHQ48	<800 (U/l)	800-2500 (U/l)	>2500 (U/l)
	n=249	n=412	n=239
Mean LDHQ (U/l)	414	1443	3939
LVef (%)	51±8*	45±9*	35±10*
Death at 1 year, n(%): all cause	2(0,8)*	10(2,4)*	22(9,2)*
cardiac	0	7(1,7)*	20(8,4)*

*p<0.001

LDHQ36	<800 (U/l)	800-2500 (U/l)	>2500 (U/l)
	n=328	n=467	n=232
Mean LDHQ (U/l)	412	1468	3777
LVef (%)	50±9*	44±9*	34±10*
Death at 1 year, n(%): all cause	4(1,2)*	12(2,6)*	20(8,6)*
cardiac	2(0,6)*	9(1,9)*	18(7,8)*

*p<0.001

Discussion

This study shows that enzymatic infarct size estimated as cumulative LDH release calculated at 72 hours, in patients treated with PCI, is closely correlated with the calculated release at 60, 48 and 36 hours. Eighty-three percent of the $LDHQ_{72}$

is already released at 36 hours after the onset of infarction. Since the benefit of reperfusion therapy is the greatest when it is started within 6 hours after onset of symptoms, we excluded patients with an ischemic time > 6 hours[26]. Classification of enzymatic infarct size in small, medium and large infarction defined as $LDHQ_{72}$ < 800 U/l, 800-2500 U/l and > 2500 U/l is a useful way to identify low, intermediate and high risk patients with regard to LVef and cardiac death at 1 year. Using the same infarct size classification, $LDHQ_{36}$ has a similar prognostic value as $LDHQ_{72}$. It has been demonstrated that the relation between global ejection fraction and LDH infarct size is maintained, regardless of whether or not reperfusion therapy is given[2,27]. Therefore, it can be assumed that our criteria for infarct size may have the same prognostic value in patients without successful reperfusion. However, the number of patients with failed angioplasty is too small in this cohort, to prove this assumption. Lactate Dehydrogenase release may continue for 96 hours after onset of infarction and in large infarctions even longer [14,15], therefore $LDHQ_{36}$ does not represent total myocardial damage. Nevertheless, the prognostic value of $LDHQ_{36}$ with regard to ejection fraction and death at 1 year, is excellent. Our data confirm that anterior infarction is associated with larger infarct size and worse clinical outcome compared with non-anterior infarction. Although longer occlusion time results in more extended myocardial damage, in our data ischemic time in patients with small, medium and large infarctions was comparable. A limitation of our study is that our population is a selected group of patients with first acute myocardial infarction undergoing early successful reperfusion. Also a limitation is that LVef was not measured in all patients. Although $LDHQ_{72}$ is only available in 36% of the total cohort, the number of patients is sufficient for a reliable statistic comparison. We have no reason to assume a selection bias occurred since baseline characteristics of $LDHQ_{72}$ were comparable with $LDHQ_{36}$, representing 96% of the total cohort.

Our study shows the possibility of early post-PCI risk stratification, by serial serum LDH detection and calculation of the cumulative release, representing small, medium and large infarction and correlation with LVef and clinical outcome. This is an easy and simple measurement and therefore applicable in the clinical chemistry

laboratories of all hospitals. Blood sampling for estimation of infarct size based on cumulative release of LDH, can be limited to 36 hours after onset of infarction, instead of 72 hours. Recent studies have shown that for patients with acute myocardial infarction presenting at hospitals without PCI facilities, transfer for urgent PCI is the best reperfusion therapy and minimises post-intervention hospital stay[16,17]. This approach requires early risk stratification at the time of discharge or transfer to the referring hospital to optimize post-intervention monitoring and treatment. In conclusion, infarct size classification by $LDHQ_{36}$ can be used as an objective, easy and simple way of early risk stratification, predicting LVef and long-term clinical outcome in patients treated with primary angioplasty for acute ST-segment elevation myocardial infarction.

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Chapter 4

Role of collateral circulation in the acute phase of ST segment elevation myocardial infarction treated with primary coronary intervention

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Abstract

AIMS: The role of collateral flow in the first hours of infarction remains unclear. Our aim was to determine whether angiographic evidence of coronary collateral flow has a beneficial effect on infarct size and left ventricular function in acute myocardial infarction (MI) treated with early percutaneous coronary intervention (PCI).

METHODS: Between 1994 and 2001, 1059 patients with acute MI treated with primary PCI, TIMI 0 or 1 flow at first contrast injection and technical adequate angiograms for collateral flow detection were analysed.

RESULTS: Comparing collateral flow grade 0, 1 and 2/3, increased collateral flow is associated with lower incidence of Killip class ≥2 at presentation (12.% versus 10% versus 3%, p for trend 0.02), decreased use of intra aortic balloon pumping post-PCI (17% versus 13% versus 5%, p for trend 0.005), better myocardial blush grade (MBG) in LAD related infarcts (MBG3: 14% versus 18% versus 34%, p for trend 0.01) and smaller enzymatic infarct size ($LDHQ_{36}$) (1932±1531 U/l versus 1870±1458 U/l versus 1217±762 U/l, p for trend 0.041). These beneficial effects are particular present in LAD related infarcts.

CONCLUSION: Presence of angiographically detectable collaterals have a protective effect on enzymatic infarct size and pre- and post-intervention hemodynamic conditions in patients with acute MI treated with primary PCI, in particular when Rentrop grade 2/3 is present and in LAD related infarcts.

Introduction

The role of collateral circulation to the myocardium at risk in the setting of acute coronary occlusion has been of special interest in the last decades. Animal studies have shown a protective effect of collateral flow on infarct size in relation to the area at risk[1,2]. In humans, angiographic studies after thrombolytic therapy showed better preservation of left ventricular function in patients with early collateral flow when reperfusion therapy had failed[3,4]. Coronary collateral flow to the infarcted area when coronary occlusion persists, tends to increase in the days and weeks following the acute event[5,6]. This late recruitment of coronary collaterals is associated with left ventricular functional recovery in patients with late mechanical infarct artery reperfusion[7,8]. Whether early coronary collateral circulation to the infarct related artery in the first hours of acute coronary occlusion has a beneficial effect on infarct size and mortality in patients with successful reperfusion therapy is yet unclear. In a selected population of patients with anterior myocardial infarction, angiographic evidence of collateral circulation was associated with better hemodynamics at presentation and lower in hospital mortality[9]. Other studies showed no clinical benefit of early collateral circulation in acute myocardial infarction treated with primary percutaneous coronary intervention (PCI) or thrombolysis[10,11]. Coronary collateral flow may be identified by several different techniques. We studied coronary collateral flow as detected by angiographic means because it is easy to incorporate in routine clinical practice of acute myocardial infarction treatment with PCI. Our aim was to determine whether early angiographic evidence of collateral circulation to the infarct related coronary artery is related to infarct size, morbidity and mortality in patients treated with PCI within 6 hours after onset of symptoms.

Methods

Patients

Between December 1994 and June 2001, 1702 patients with ST segment elevation myocardial infarction (MI) and symptoms lasting < 6 hours were treated with PCI. In 860 patients the diagnosis of acute MI was established at the patient's home by the ambulance crew or at the emergency department of the referring hospital. These patients received aspirin (500 mg intravenously) and heparin (≥ 4,000 IU intravenously) before transportation to our hospital. In 842 patients, the diagnosis of acute MI was established in the emergency room of our hospital. These patients received aspirin and heparin intravenously in the emergency room and were transported immediately to the catheterization laboratory. None of these patients received fibrinolytic therapy or glycoprotein IIb-IIIa blockers before PCI[12].

We excluded patients with left main and venous graft related infarcts and patients with anterograde flow in the infarct related artery at first contrast injection[13]. In 178 patients, collateral flow could not be graded for technical reasons. We included 1059 patients with Thrombolysis in Myocardial Infarction (TIMI) flow 0 or 1, details regarding other inclusion and exclusion criteria have previously been published[14,15]. Inclusion criteria were symptoms of acute myocardial infarction that persisted for more than 30 minutes, with more than 1 mm (0.1 mV) ST segment elevation in two or more contiguous electrocardiographic leads. Coronary angiography was performed as quickly as possible.

Collateral flow from the patent vessels to the infarct related artery was graded according to the classification developed by Rentrop[16]. Grade 0: no visible filling of any collateral channel, grade 1: filling of side branches of the occluded artery with no dye reaching the epicardial segment, grade 2: partial filling of the epicardial vessel, grade 3: complete filling of the epicardial vessel by collateral vessels. Both TIMI flow and myocardial blush were graded on the angiograms made immediately after the primary coronary angioplasty procedure, by two experienced investigators, who were blinded to all data apart from the coronary angiograms. Arterial patency was

determined as TIMI grade 3 flow. Myocardial blush grade (MBG) was graded according to the classification described earlier[17]. Grade 0: no myocardial blush or contrast density, grade 1: minimal myocardial blush, grade 2: moderate myocardial blush and grade 3: normal myocardial blush. The indication for intra–aortic balloon pumping (IABP) was made by the operator based on hemodynamic and clinical parameters. Left ventricular ejection fraction (LVef) was measured within 1 week post MI with a radionuclide technique, as described earlier[14]. Left ventricular function may improve over time after acute MI treated with early reperfusion therapy due to functional recovery of stunned myocardium[18]. Therefore LVef at follow-up was measured at 6 months post MI. Infarct size was measured by calculation of cumulative Lactate Dehydrogenase release at 36 hours after symptom onset ($LDHQ_{36}$)[19]. Samples were obtained on admission and every 12 hours up to 36 hours. From these measurements, an area under the curve was calculated. These measurements and calculations were performed at the department of clinical chemistry, without access to the clinical data. Based on collateral flow grade at first contrast injection in the contralateral coronary artery, patients were divided in 3 groups; Rentrop grade 0, grade 1 and grade 2/3 group. All data were analysed by an independent core laboratory (Diagram, Zwolle, The Netherlands)

Statistical analysis

In our presentation of the data, continuous baseline and outcome variables are given as means ± SD, whereas discrete variables are given as absolute values and percentages. Patients were divided in 3 groups based on the degree of collateral flow. Trend analyses were performed, adjusted for infarct related artery (LAD versus non-LAD). When the interaction between flow and artery was significant, separate analyses for LAD and non-LAD related infarcts were performed. Linear, logistic and proportional hazard regression was used for the trend analysis of the continuous, discrete, respectively survival variables. The fit of the various models was assessed by inspection of the raw means (and distribution), raw log(odds) and log(-log) plots, respectively. Only for $LDHQ_{36}$ a possible lack of fit was observed, but as additional

analyses produced similar results, the outcome of the originally planned method is reported. Survival rates were calculated by Kaplan-Meier analysis. Differences for the main effects were considered statistically significant at $p < 0.05$ (two-sided test). In total, 6 outcome measures were analyzed, and 3 statistically significant results were found. As no adjustment was made, the total error rate may exceed 0.05. This approach was chosen in view of the explorative character of the study. Interactions were considered statistically significant at the 15% significance level.

Table 1. Baseline characteristics

	Rentrop 0 N=562	Rentrop 1 N=391	Rentrop 2/3 N=106	*p for trend*
Age, (year)	59±11	60±11	59±13	*0.843*
Male, n(%)	464(83)	302(77)	88(83)	*0.497*
Diabetes, n(%)	40(7)	30(8)	5(5)	*0.575*
Hypercholesterolaemia, n(%)	91(16)	64(16)	22(21)	*0.494*
Hypertension, n(%)	124(22)	93(24)	26(25)	*0.426*
Smoking, n(%)	276(49)	199(51)	51(48)	*0.878*
Family History for CAD, n(%)	215(38)	160(41)	45 (43)	*0.343*
Previous MI, n(%)	62(11)	34(9)	14(13)	*0.731*
Previous revascularisation, n(%)	32(6)	23 (6)	11(10)	*0.276*
MVD, n(%)	307(55)	204(52)	55(52)	*0.261*
Ischemic time, (min)	195±67	194±69	209±69	*0.224*
TIMIpost 3, n(%)	512(91)	359(92)	97(92)	*0.875*
IRV : LAD, n(%)	291(52)	183(47)	35(33)	*0.001*

CAD: coronary artery disease, MI: myocardial infarction, MVD: multi vessel disease, TIMIpost 3: TIMI flow grade 3 post angioplasty, IRV: infarct related artery

Results

A total of 1059 patients with a total coronary occlusion during initial coronary angiography were included in the analysis. All patients presented within 6 hours after onset of symptoms. Thirty-day follow-up was completed in all patients and 1 year follow-up in 881(83%) patients. LVef was the first time measured in 854(81%) patients at 4±6 days post MI and a second time in 463(44%) patients at 190±31 days

post MI. Complete LDHQ36 was available in 810(76%) patients. Rentrop grade 3 flow was present in only 7 patients. So in the analyses Rentrop grade 2 and 3 were merged. Baseline characteristics are shown in table 1. Early collateral recruitment is more often present in patients with a non-LAD related infarct than in patients with a LAD related infarct. No differences were seen in the prevalence of risk factors for coronary artery disease, previous coronary events or previous revascularisation procedures, the presence of multi vessel disease or success or failure of the PCI procedure.

Table 2. Outcome measures

	Rentrop 0 N=562	Rentrop 1 N=391	Rentrop 2/3 N=106	*p for trend*
$LDHQ_{36}$, (U/l)	1932±1531	1870±1458	1217±762	*0.041*
MBG 3, n(%)	122(22)	100(26)	31(29)	*0.154**
Killip≥2, n(%)	65(12)	38(10)	3(3)	*0.022*
IABP, n(%)	95(17)	49(13)	5(5)	*0.005*
LVef1, (%)	43±11	43±11	46±9	*0.616*
LVef2, (%)	46±11	46±11	47±10	*0.962*

$LDHQ_{36}$: enzymatic infarct size, MBG 3: myocardial blush grade 3, IABP: intra aortic balloon pump, LVef1: left ventricular ejection fraction within 1 week post MI, LVef2: left ventricular ejection fraction at 6 months post MI

*Significant interaction between flow and artery was observed (p=0.034), separate analyses for LAD and non-LAD are presented in table 3.

Table 2 shows the outcome measures. The higher the grade of Rentrop collaterals, the lower the Killip class rate on admission. In patients with collateral flow grade 2/3, enzymatic infarct size is smaller compared to patients with grade 1 or no collateral flow (1932±1531 U/l versus 1870±1458 U/l versus 1217±762 U/l, p for trend 0.041). The presence and extent of collateral flow is associated with a decreased use of intra-aortic balloon pumping (IABP) post PCI (17% versus 13% versus 5%, p for trend 0.005). In the adjusted analyses for LAD and non-LAD related infarcts, we first evaluated interaction, which was only significant for MBG3 (p=0.034). So a separate analysis for LAD and non-LAD was performed (table 3). The higher the grade of Rentrop collaterals to an occluded LAD, the higher the incidence of normal myocardial blush (MBG3) (Rentrop 0: 14% versus Rentrop 1: 18% versus Rentrop

2/3: 34%, p for trend 0.01). Collateral flow to an occluded non-LAD does not influence the incidence of normal myocardial blush. One-year survival rates were 95% versus 96.2% versus 97.2% for Rentrop grade 0, 1, 2/3 respectively (p=0.66). The hazard ratio's, adjusted for LAD or non-LAD, for patients with Rentrop grade 2/3 versus Rentrop grade 0 was 1.54 (95%CI: 0.47-5.26; p=0.47).

Table 3. Myocardial blush grade 3 for LAD and non-LAD related infarcts

	Rentrop 0	Rentrop 1	Rentrop 2/3	*p for trend*
LAD	N=291	N=183	N=35	
MBG3, n(%)	42(14)	33(18)	12(34)	*0.01*
Non-LAD	N=271	N=208	N=71	
MBG3, n(%)	80(30)	67(32)	19(27)	*0.933*

MBG3: myocardial blush grade 3

Discussion

This study shows in patients with acute ST segment elevation myocardial infarction, treated with PCI early after the onset of symptoms, that collateral circulation Rentrop grade 2/3 to the occluded coronary artery is associated with better microvascular reperfusion of the myocardium, as reflected by a higher incidence of normal myocardial blush after PCI in LAD related infarcts and smaller enzymatic infarct size. Furthermore, patients with grade 2/3 collateral flow presented in lower Killip class and less often needed support from an IABP post intervention. Early collateral recruitment is more frequently present in patients with acute non-LAD occlusion, suggesting a more extensive collateralisation from the LCA to the RCA.

After successful restoration of anterograde flow in the LAD, Rentrop grade 2/3 collateral flow is associated with a better microvascular perfusion of the myocardium represented as a higher incidence of normal myocardial blush. This beneficial effect of collateral flow is not seen in the non-LAD related infarcts. In patients with persistent coronary occlusion, collateral development increases in the

days and weeks following the acute occlusion. Our study shows that even in the first 6 hours following acute coronary occlusion, collateral flow may increase considerably over time. Experimental studies have shown that after coronary occlusion, collateral flow to the centre of the infarct zone was the lowest at the base of the left ventricle and increased toward the apex, resulting in relatively greater salvage of jeopardised myocardium from base to apex[21]. Also is shown that the extent of intact myocardium between the lateral and epicardial edge of the risk area and transmural necrosis is markedly broader in the interventricular septum than in the left ventricular free wall[22].

Since the LAD pre-dominantly perfuses the interventricular septum and apex, these physiologic characteristics could be an explanation for our finding that adequate collateral flow mainly shows a protective effect to an acutely occluded LAD. In patients with anterior infarction the area of jeopardised myocardium is larger than in patients with inferior infarction [23].So although our results show an absence of a protective effect on the microvascular perfusion of collateral flow to acutely occluded non-LAD related infarcts, there is still a possibility that this effect is present but that the detection of this protective effect is problematic due to the smaller area at risk. These data are the first to support the suggestion that the presence of collateral flow plays an important role in sustaining jeopardised myocardium until reperfusion is accomplished, even in the first hours after acute coronary occlusion.

Angiographic collateral flow detection provides only an estimate of the absolute collateral flow that may be present since only collaterals > 100 μm in diameter are identified. Despite this limitation, the association of collateral flow grade 2/3 with a higher incidence of normal myocardial blush and smaller enzymatic infarct size after early PCI of an occluded LAD are parameters for the presence of adequate collateral flow on arteriolar and myocardial level. Other techniques for collateral flow detection like myocardial contrast-echocardiography, radionuclide techniques and pressure-derived collateral flow index are indirect methods with better quantification of collateral flow[7,24,25]. Unfortunately these methods are not easy to incorporate in routine daily clinical practice in acute myocardial infarct treatment

with PCI. A limitation of our study is that our population is a selected group of patients with first acute myocardial infarction undergoing mechanical reperfusion early after the onset of symptoms. Another limitation is that LVef and $LDHQ_{36}$ could not be measured in all patients.

In conclusion, the presence of angiographically detectable collaterals have a protective effect on enzymatic infarct size, microvascular perfusion of the myocardium and pre- and post-interventional hemodynamic conditions in patients with acute ST segment elevation myocardial infarction treated with PCI, in particular when Rentrop grade 2/3 is present and the LAD is the infarct related vessel.

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Chapter 5

Impact of infarct location on left ventricular ejection fraction after correction for enzymatic infarct size in acute myocardial infarction treated with primary coronary intervention

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Abstract

BACKGROUND: Left ventricular function and infarct size are strong predictors for prognosis after acute myocardial infarction (MI). Anterior MI is associated with greater reduction of left ventricular ejection fraction (LVef) and worse prognosis. Our objective was to study whether the impact of infarct size on global LVef is dependent of infarct location.

METHODS: We analysed 888 patients treated with primary percutaneous coronary intervention (PCI) for acute MI. Enzymatic infarct size (LDHQ36) and LVef within 1 week were measured. In 490(55%) patients, LVef was measured a second time at 6 months.

RESULTS: Every 1000 U/l cumulative LDH release corresponded to a decrease of 4.7% (95% CI 4.1-5.3) in LVef measured within 1 week post-MI for LAD related infarcts and to a decrease of 2.4% (95% CI 1.7-3.1) in LVef measured within 1 week post-MI for non-LAD related infarcts, $p < 0.0001$. LVef measured 6 months post-MI showed a decrease for every 1000 U/l cumulative LDH release of 4.8% (95% CI 4.2-5.3) for LAD and 2.4% (95% CI 1.7-3.1) for non-LAD related infarcts, $p<0.0001$. Multivariate correction for relevant clinical and angiographic data did not change these results.

CONCLUSION: In patients with a first acute MI treated with primary PCI, LAD related infarcts have a lower residual LVef when compared with non-LAD related infarcts, for a similar amount of myocardial necrosis as determined by enzymatic infarct size.

Introduction

Left ventricular function is a strong predictor of prognosis after acute myocardial infarction (MI)[1,2]. A major determinant of left ventricular function is the size of infarction. Enzymatic infarct size, when estimated as cumulative LDH release, is thought to represent total myocardial cell death and is related to left ventricular ejection fraction (LVef) after first myocardial infarction[3,4]. Anterior infarcts are associated with a larger enzymatic infarct size and greater reduction in LVef compared to non-anterior infarcts[5]. However it is unknown whether infarct size alone is the only mechanism to explain the worse prognosis of anterior infarction. Possibly other factors, related to the specific distribution area of the left anterior descending coronary artery (LAD) may play a role. Experimental studies in animals show a greater reduction in radionuclide LVef after LAD occlusion compared with occlusion of the ramus circumflexus (CX) with comparable histologic size[6]. In patients with a first MI treated without reperfusion therapy, prognosis is worse for anterior compared to inferior infarction of similar infarct size estimated as peak CK[5,7]. A recent study showed lower LVef in patients with anterior compared with inferior infarction of similar echocardiographic infarct size[8]. These studies have all been done in humans and animals with persistent occlusion of the infarct related artery and left ventricular function was measured within 1 week post-infarction, when myocardial stunning is thought to be still present. Early reperfusion reduces infarct size, preserves left ventricular function and prevents remodeling. Therefore we examined whether the site of coronary occlusion has an influence on the relation between enzymatic infarct size and LVef at 1 week and at 6 months post-infarction in patients with first acute ST segment elevation MI treated with early primary PCI.

Methods

Between December 1994 and June 2001, 1702 consecutive patients with ST segment elevation MI and symptoms lasting < 6 hours were treated with primary PCI. Our study was approved by the Institutional Review Board and performed in a single centre. Analysis were performed by an independent core laboratory (Diagram, Zwolle, the Netherlands) blinded to all clinical data and outcome. Details regarding other inclusion and exclusion criteria have been published[9,10]. Inclusion criteria were symptoms of acute MI that persisted for more than 30 minutes, with more than 1 mm (0,1 mV) ST segment elevation in two or more contiguous electrocardiographic leads. To determine the relation between the actual infarct size and ventricular function, we excluded patients with a previous MI (200 patients) and patients with a left main or bypass graft as infarct artery (30 patients), leaving 1472 patients. Only patients with both enzymatic infarct size and LVef measured were included for analysis.

All patients received aspirin (500 mg intravenously), heparin (> 4000 IU intravenously) and nitroglycerin intravenously in a dose designed to maintain a systolic blood pressure of 110 mmHg. LVef was measured with a radionuclide technique within 1 week and at 6 months post-infarction, as described earlier[9]. Enzymatic infarct size was estimated by calculation of cumulative Lactate Dehydrogenase release up to 36 hours after symptom onset ($LDHQ_{36}$), as described earlier[11]. In summary blood samples were drawn on admission and after 3, 12, 24 and 36 hours. LDH activity was determined enzymatically on a Hitachi 717 automatic analyzer according to the International Federation of Clinical Chemistry (IFCC) recommendation at 30°C[6]. Reference values for LDH are < 320 U/l (adults). Infarct size was estimated by measurements of enzyme activities using LDH as the reference enzyme. This method is equal to estimation of infarct size from α-hydroxybutyrate (HBDH) and has been described in detail[12,13]. Cumulative enzyme release was calculated at 36 hours at the department of clinical chemistry with blinding to all data other than hospital registration number and date of birth. Coronary angiography and PCI of the infarct related artery was performed using standard techniques. Arterial patency was

defined as Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow of the infarct related artery[14]. Ischemic time was determined as time between onset of symptoms and first balloon inflation. Patients were divided in groups according to native infarct related artery: left anterior descending(LAD), right coronary artery(RCA) and ramus circumflexus(CX).

Table I. Baseline characteristics

	non-LAD n=456	LAD n=432	*p*
Age (year)	60±12	59±11	*0.268*
Male, n(%)	355(78)	359(83)	*0.049*
Ischemic time (min.)	195±68	191±66	*0.408*
Diabetes, n(%)	43(9)	29(7)	*0.092*
Hypertension, n(%)	100(22)	92(21)	*0.819*
Hypercholesterolaemia, n(%)	85(19)	59(14)	*0.044*
Family history, n(%)	186(41)	156(36)	*0.152*
Prior smoker, n(%)	220(48)	217(50)	*0.554*
TIMIpre 0+1, n(%)	356(78)	318(74)	*0,12*
TIMIpost 3, n(%)	422(93)	393(91)	*0.394*
MVD, n(%)	253(56)	179(41)	*<0.001*
MBG2/3, n(%)	378(83)	300(69)	*<0.001*
Killip≥2, n(%)	27(6)	51(12)	*0.002*
RRsyst (mmHg)	132±30	133±42	*0.512*
RRdiast (mmHg)	78±18	78±18	*0.911*
Heartrate(min^{-1})	71±19	77±19	*<0.001*
Prev. Revascularisation, n(%)	26(6)	11(3)	*0.019*
Collaterals, n(%)	175(38)	134(31)	*0.021*

TIMIpre 0+1: TIMI flow 0 or 1 before intervention, TIMIpost 3: TIMI flow 3 after intervention, MVD: multi vessel disease, MBG 2/3: myocardial blush grade 2 or 3

Statistical analysis

The SPSS 10.1 program was used for data analysis. In our presentation of the data, continuous baseline and outcome variables are given as means ± SD, whereas discrete variables are given as absolute values and percentages. Differences between group means were assessed by the Pearson Chi-square test. Mann-Whitney U test was used to test differences between proportions. A linear regression model was used to compare baseline, clinical and angiographic variables associated with post MI

LVef. Variables with a p value < 0.15 in the univariate analyses were entered into a multivariate regression model. Differences were considered significant at $p < 0.05$.

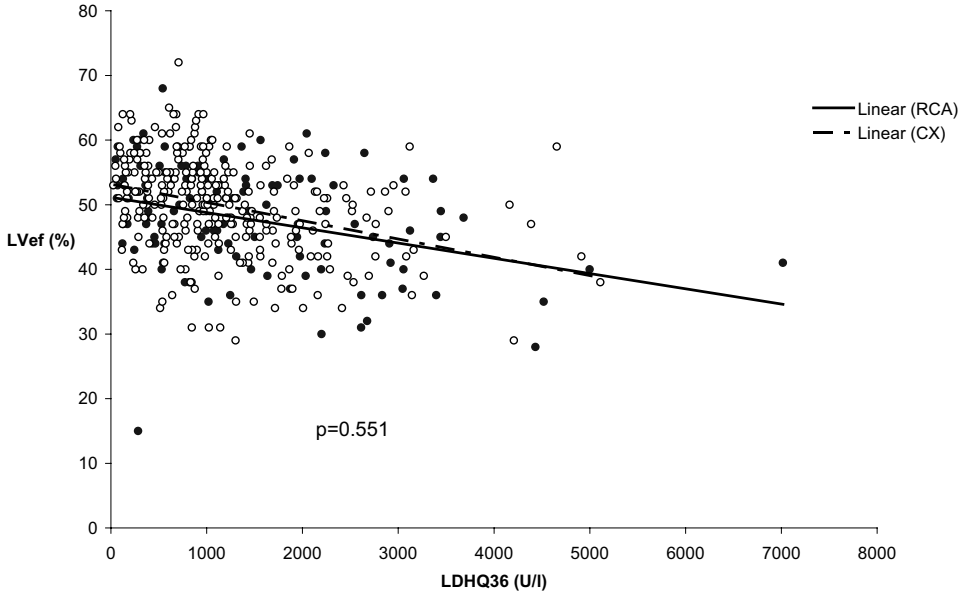

Figure 1: Correlation of LDHQ36 and LVef at 1 week post-MI for RCA and CX related infarcts

Results

From a total of 1472 patients, $LDHQ_{36}$ was measured in 1193 (81%) patients and LVef was measured within 1 week in 959 (65%) patients, both measurements were available in 888 patients. These patients form the basis of this analysis. In 279 patients $LDHQ_{36}$ was not measured, in 14 patients due to death within 36 hours post-MI. In 305 patients $LDHQ_{36}$ was measured but LVef1 was not, in 11 patients due to death within 1 week post-MI. Groups were divided according to the infarct related artery. In all 888 study patients LVef was measured within 1 week post-MI and in 490 (55%) patients LVef was measured a second time at 6 months post-MI. In 8 patients LVef could not be measured a second time due to death between 1 week and 6 months post-MI. Baseline characteristics are shown in table I.

Table II. Left ventricular ejection fraction at 1 week and 6 months post-infarction in LAD and non-LAD related infarcts

	LAD	non-LAD	*p*
	N=432	N=456	
Lvef1 (%)	39±11	49±8	*<0.001*
	N=241	N=249	
Lvef2 (%)	43±11	51±9	*<0.001*
p	*<0.0001*	*0.01*	

LVef1: left ventricular ejection fraction at 1 week post MI

LVef2: left ventricular ejection fraction at 6 months post MI

In table II is shown that in patients with LAD related infarcts, LVef within 1 week post-MI is lower compared to non-LAD related infarcts. At 6 months LVef is significantly increased in both groups but remains lower in the LAD related infarcts. Linear regression for enzymatic infarct size and LVef at 1 week post-MI showed that in LAD related infarcts every 1000 U/l cumulative LDH release corresponded to a decrease of 4.7% (95% CI 4.1 – 5.3, p<0.0001) in LVef. In the non-LAD related infarcts every 1000 U/l cumulative LDH release corresponded to a decrease of 2.4% (95% CI 1.7 – 3.1, p<0.0001) in LVef. This difference between LAD and non-LAD related infarcts is significant with a p value < 0.0001. Inclusion of the variables male gender, diabetes mellitus, heart rate, Killip class≥2 at presentation, multi vessel disease, TIMI flow 0 or 1 pre-intervention, TIMI flow 3 post-intervention and myocardial blush grade 2 or 3 in a multivariate regression model did not change these results. Linear regression for enzymatic infarct size and LVef at 6 months post-MI showed comparable results with a decrease of 4.8% (95% CI 4.2 – 5.3, p<0.0001) in LVef for every 1000 U/l cumulative LDH release in LAD related infarcts and with a decrease of 2.4% (95% CI 1.7 – 3.1, p<0.0001) in LVef for every 1000 U/l cumulative LDH release in non-LAD related infarcts (p<0.0001). Multivariate regression analyses with the same variables as mentioned above did not change these results. In figure 1 is shown that the correlation between enzymatic infarct size and LVef for RCA and CX related infarcts is similar (p=0.55). Figure 2 and 3 show the correlation between enzymatic infarct size and LVef at 1 week and 6 months post-MI in LAD and non-LAD related infarcts.

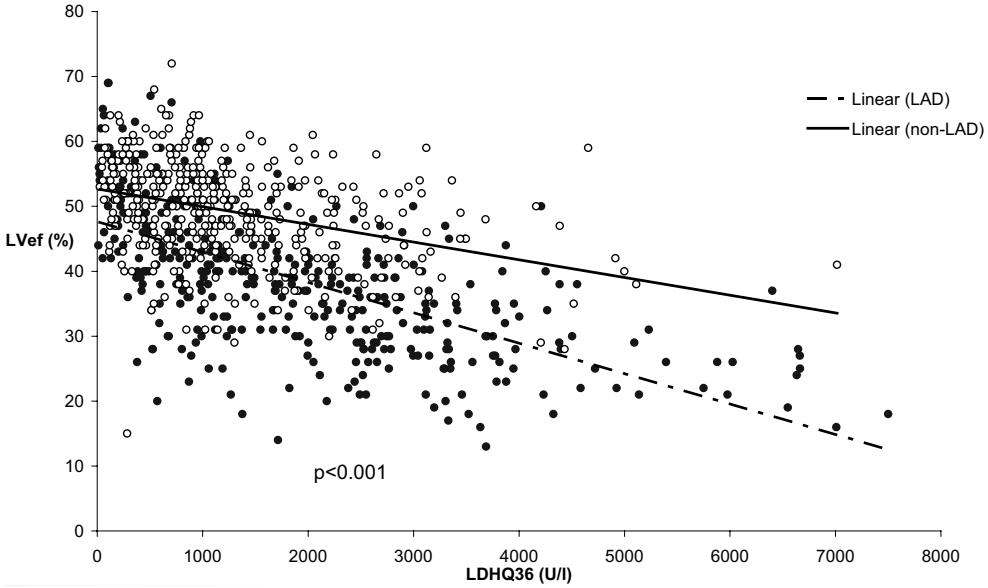

Figure 2. Correlation of LDHQ36 and LVef at 1 week post-MI for LAD and non-LAD related infarcts

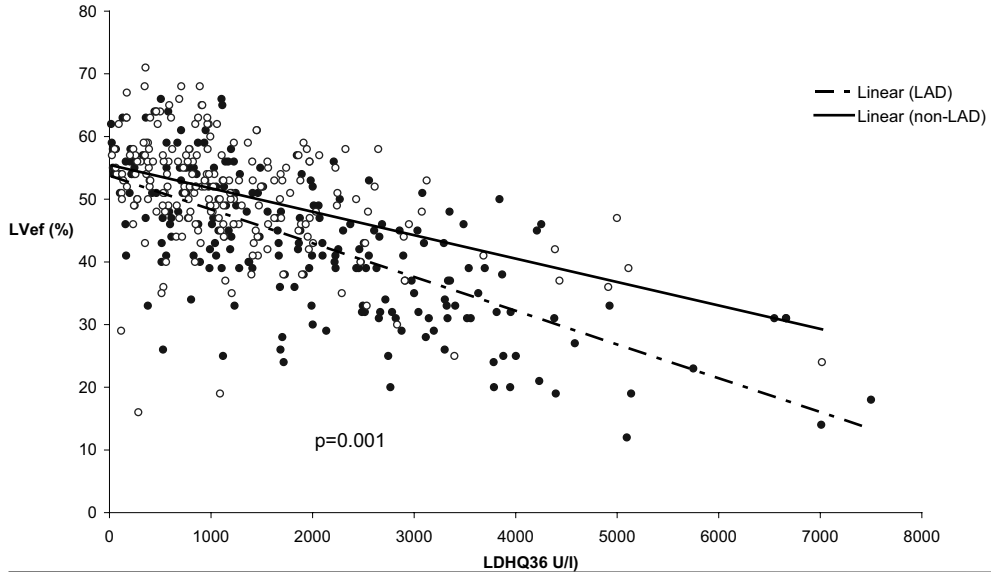

Figure 3. Correlation of LDHQ36 and LVef at 6 months post-MI for LAD and non-LAD related infarcts

Discussion

This is the first analysis comparing the relation between enzymatic infarct size and LVef stratified for the native infarct related coronary artery in patients with a first acute MI treated with primary PCI. Our results show that for a given amount of myocardial cell loss, LVef at discharge is lower in LAD related infarcts as compared to non-LAD related infarcts. Despite the overall increase in LVef at 6 months post-MI, this difference remains present, and multivariate analysis for relevant baseline characteristics does not have an impact on this finding.

Until now studies investigating the relation between infarct size, infarct location and left ventricular function have not been able to show the relation between actual infarct size and left ventricular function when early reperfusion therapy is administered for acute MI, this may be due to the following reasons[5-8].

The previous studies were performed in patients with chronic occluded infarct arteries in which remodeling is a major cause of left ventricular detoriation. This occurs mainly in antero-apical infarction[15-17]. Furthermore the possible influence of stunned myocardium on LVef could not be excluded, since indirect infarct size measurements were used and left ventricular function was measured within 1 week post-MI. To rule out the possible influence of stunned myocardium we used LDHQ36 as representing the actual size of infarcted myocardium and we measured the LVef a second time at 6 months[3,18].

Many studies have shown that LAD related infarcts have a worse prognosis when compared to non-LAD related infarcts[15,19]. This is thought to be mainly due to the increased muscle mass at risk and to a lower likelihood of achieving normal myocardial perfusion despite restored epicardial flow, resulting in a larger amount of damaged myocardium[20]. The severity of damage of the myocardium is often quantified by measurement of the LVef[21]. Our study shows that the quantification of infarct size by LVef does not represent the same amount of myocardial necrosis for LAD and non-LAD related infarcts. Other factors, known to be related to a lower residual LVef and worse prognosis are MVD, TIMI pre flow grade 0 or 1, TIMI post

flow grad<3, MBG grade < 2, absence of coronary collateral flow, Killip class ≥2 on admission, diabetes mellitus and ischaemic time. We corrected for these factors in our multivariate analyses. This did not change the site dependent difference in the impact of a given amount of myocardial damage on the residual LVef between LAD and non-LAD related infarcts. Therefore, the worse prognosis of LAD related infarcts is not only related to a larger amount of necrosed myocardium but also to specific characteristics of this infarct location. The LAD mostly perfuses the left ventricular apex, anterior wall and inter-ventricular septum. The RCA and CX mostly perfuse the left ventricular base and free wall. Left ventricle shortening is characterized by regional differences with greater hoop axis shortening near the apex[22]. The myocardium at the apex of the left ventricle is thinner compared with the base due to lacking of circumferential fibers of the middle myocardial layer[23,24]. Ischemia induces further thinning and fiber lengthening leading to a more rapid rise in regional wall stress at the apex compared with the base resulting in an exaggerated difference in regional dilation. These regional structural differences of the myocardium may be a potential explanation for our findings.

Limitations

A limitation of our study is that LVef and enzymatic infarct size was measured in a subset of all infarct patients, however baseline characteristics were comparable. The main reason for missing $LDHQ_{36}$ or LVef measurement is that these patients were transferred from another hospital for primary PCI and were transferred back before $LDHQ_{36}$ or LVef could be measured. Glycoprotein IIb-IIIa inhibitors have only been used in 5% of our population[25]. Furthermore no distal protection devices have been used in this series of patients. We have no data with regard to the pre-infarct left ventricular function but since we only included patients with a first MI we have no reason to assume a difference between the two groups.

Clinical implications

Patients with LAD related infarcts have worse clinical outcome compared to non-LAD related infarcts[26], which is related to a lower residual LVef[21]. Up till now the lower residual LVef in LAD related infarcts is thought to be solely due to the larger final infarct size. Multiple previous studies have shown that clinical outcome in acute MI was better in patients treated with primary PCI when compared with thrombolysis, even when patients need to be transported for treatment[9,27-29]. Our data show that not only infarct size but also the specific location of LAD related infarcts play an important role in the lower post-infarct LVef. Since especially in LAD related infarcts LVef is a strong independent predictor of long-term mortality our data make it better understandable why LAD related infarcts benefit in particular from primary PCI[30].

Conclusion

In conclusion our data show that in patients with a first acute MI treated with primary PCI, LAD related infarcts show for a similar amount of myocardial necrosis, as measured by enzymatic infarct size, a lower residual pre-discharge LVef when compared with non-LAD related infarcts. Although LVef at 6 months post-MI increases independent of infarct location, this difference remains present.

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Chapter 6

Effect of coronary occlusion site on angiographic and clinical outcome in acute myocardial infarction patients treated with early coronary intervention

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Abstract

In acute myocardial infarction (AMI) treated with thrombolysis, proximal coronary artery occlusion is associated with worse prognosis, irrespective of the infarct artery. Nowadays primary percutaneous coronary intervention (PCI) is the treatment of choice for ST-segment elevation AMI. Therefore we evaluated the prognostic significance of proximal versus distal coronary artery occlusion in patients with AMI treated with primary PCI. Between 1994 and 2001, patients with a first AMI treated with primary PCI were analysed. A lesion was considered proximal if it was located proximal to the first diagonal branch in the left anterior descending artery (LAD), the first marginal obtuse branch in the left circumflex and the first right acute marginal branch in the right coronary artery. Lesions distal of these side-branches were considered distal. A total of 1468 patients were analyzed. Left ventricular ejection fraction (LVef) for proximal LAD was lower when compared with distal LAD lesions (37±11% versus 42±11%, $p<0.0001$). Adjusted relative risk of 3-year mortality for proximal versus distal LAD was 4.04 (95% CI 1.95 – 8.38). In patients with right coronary artery or left circumflex related infarcts no significant association between lesion location and LVef or mortality was seen. No difference is seen in adjusted 3-year mortality between distal LAD and non-LAD related infarcts ($p=0.145$). Our analysis shows that even in patients with AMI treated with primary PCI, infarcts related to the proximal LAD have the worst 3-year survival and lowest residual LVef when compared with distal LAD or non-LAD related infarcts.

Introduction

In patients with acute myocardial infarction (AMI) the primary objective of therapy is aimed on restoring blood flow in the infarct related coronary artery[1]. Reperfusion can be obtained by thrombolysis or primary percutaneous coronary intervention (PCI). Several studies have demonstrated a better survival in patients with AMI treated with primary PCI, when compared to thrombolysis, even when patients have to be transported for treatment [2-5]. Irrespective the given reperfusion therapy important prognostic factors are infarct location, infarct size and residual left ventricular function[6]. Compared to non-left anterior descending artery (LAD) related infarcts, LAD related infarcts have worse clinical outcome due to lower residual left ventricular ejection fraction (LVef), which is related to larger final infarct size[7-9]. In right coronary artery related infarcts involvement of the right ventricle is associated with worse prognosis in the pre-reperfusion era and in patients treated with thrombolysis as reperfusion therapy[10-13]. Left circumflex artery (LC) related infarcts have a good prognosis after early reperfusion. However in LC related infarcts, proximal culprit lesions have a worse prognosis in patients treated with thrombolysis when compared with distal culprit lesions [13]. The aim of our study was to evaluate whether a proximal culprit lesion location in a given epicardial artery, which subtends a larger area of myocardium, is associated with worse prognosis when compared to a distal culprit lesion in AMI treated with primary PCI.

Table 1. Baseline characteristics

Occlusion site	proximal (n=793)	distal (n=675)	
Age (year)	61±11	58±12	<0.001
Men	616(78%)	546(81%)	0.131
Diabetes mellitus	63(8%)	56(8%)	0.806
Hypercholesterolaemia	111(14%)	126(19%)	0.015
Family history	319(40%)	264(39%)	0.663
Smoker	372(47%)	340(50%)	0.186
Hypertension	170(21%)	165(24%)	0.171
Previous revascularisation	28(4%)	23(3%)	0.898
Ischemic time (minutes)	190±66	199±68	0.038

Hypercholesterolaemia was defined as ≥ 6,5 mmol/l

Methods

We performed a single centre study. The protocol was reviewed and approved by our Institutional Review Board. Between December 1994 and June 2001, 1702 consecutive patients with ST segment elevation AMI and symptoms lasting < 6 hours were treated with primary PCI. In 860 patients the diagnosis of AMI was established at the patient's home by the ambulance crew or at the emergency department of the referring hospital. These patients received aspirin (500 mg intravenously) and heparin (≥ 5,000 IU intravenously) before transportation to our hospital. In 842 patients, the diagnosis of AMI was established in the emergency room of our hospital. These patients received aspirin and heparin intravenously in the emergency room and were transported immediately to the catheterization laboratory.

None of these patients received fibrinolytic therapy or glycoprotein IIb/IIIa blockers before PCI[14]. A stent was used in 617(42%) of the patients. After the primary PCI all patients received oral aspirin (80-100mg daily) and if a stent was implanted additional ticlopidine (250 mg/day) or clopidogrel (after june 1999; 300mg loading dose followed by 75 mg/day) was received for 4 weeks. In our analysis we excluded patients with left main or coronary bypass graft as infarct artery (54) and patients with a previous AMI (180). Details regarding other inclusion and exclusion criteria have been published[2,15]. Inclusion criteria were symptoms of acute myocardial

infarction that persisted for more than 30 minutes, with more than 1 mm ST segment elevation in two or more contiguous electrocardiographic leads. LVef was measured with a radionuclide technique within 6 months post infarction, as described earlier[2]. Enzymatic infarct size was estimated by calculation of cumulative Lactate Dehydrogenase release up to 36 hours after symptom onset as described earlier[16].

Coronary angiography and PCI of the infarct related artery was performed as quickly as possible. Arterial patency was described as Thrombolysis in Myocardial Infarction grade 3 flow of the infarct related artery[17]. Ischemic time was determined as time between onset of symptoms and first balloon inflation. Myocardial blush grade was assessed visually on the angiogram made immediately following the primary PCI and was graded according to the classification described earlier[18]. Grade 0: no myocardial blush or contrast density, grade 1: minimal myocardial blush or contrast density, grade 2: moderate myocardial blush or contrast density but less than that obtained during angiography of a contra or ipsilateral non-infarct related coronary artery and grade 3: normal myocardial blush or contrast density, comparable with that obtained during angiography of a contralateral or ipsilateral non-infarct related coronary artery. When myocardial blush persisted ("staining"), this phenomenon suggested leakage of contrast medium into the extra vascular space and was graded 0. The angiographic run had to be long enough to allow some filling of the venous coronary system, and backflow of the contrast agent into the aorta had to be present to be certain of adequate contrast filling of the epicardial coronary artery. The myocardial blush grade was assessed in the left lateral view when the left coronary artery was involved and in the right oblique view when the right coronary artery was involved. Patients were divided in groups according to location of the infarct related lesion as follows. A lesion was considered proximal if it was located proximal to the first diagonal branch in the LAD, the first marginal obtuse branch in the LC and the first right acute marginal branch in the right coronary artery. All lesions distal of the first diagonal, first marginal obtuse and first right acute marginal branch were considered distal. Our primary endpoint was all cause mortality and our secondary endpoint was residual LVef and enzymatic infarct size. We also analysed hemodynamic and angiographic outcome measures.

Table 2. Hemodynamic and angiographic outcome

Infarct Coronary Artery	Right			Left Circumflex			Left Anterior Descending		
Occlusion site	proximal	distal	p	proximal	distal	p	proximal	distal	p
	(n=316)	(n=197)		(n=79)	(n=113)		(n=398)	(n=365)	
Killip class ≥2 at presentation	34(11%)	9(5%)	0.014	8(10%)	4(4%)	0.064	70(18%)	21(6%)	<0.0001
TIMI flow pre-PCI grade 0 or 1	251(79%)	150(76%)	0.381	57(72%)	87(77%)	0.446	275(69%)	255(70%)	0.818
TIMI flow post-PCI grade 3	298(94%)	179(91%)	0.138	75(95%)	100(86%)	0.122	357(90%)	341(93%)	0.066
Myocardial blush grade 2 or 3	264(84%)	166(84%)	0.830	60(76%)	84(74%)	0.799	275(69%)	176(76%)	0.045
Multi vessel disease	178(56%)	106(54%)	0.576	50(63%)	59(52%)	0.127	167(42%)	163(45%)	0.452
Intra aortic balloon pump	19(6%)	15(8%)	0.478	6(8%)	4(4%)	0.213	102(26%)	46(13%)	<0.0001

Statistical analysis

The SPSS 10.1 program was used for data analysis. In our presentation of the data, continuous baseline and outcome variables are given as means ± SD, whereas discrete variables are given as absolute values and percentages. Differences between group means were assessed with the Mann-Whitney U test. Pearson Chi-square test was used to test differences between proportions. The association between proximal and distal occlusion site and mortality was evaluated using the Cox proportional-hazards model. The odds ratio for LAD related infarcts was corrected for variables considered confounders of the examined association. Cumulative survival curves were constructed according to the Kaplan-Meier method. All p-values were two-sided and values <0.05 were considered statistically significant.

Results

A total of 1468 patients were included for analysis. Groups were divided according to occlusion site. LVef was measured in 1065 (73%) patients within 6 months post-infarction. Enzymatic infarct size was measured in 1188 (81%) patients. Baseline characteristics are shown in table 1. Patients with proximal culprit lesions in AMI are be older and have a lower incidence of hypercholesterolemia. Hemodynamic and angiographic measures, are shown in table 2. In all coronary arteries proximal culprit lesion are associated with a higher Killip class at presentation compared with distal culprit lesions. Proximal LAD culprit lesions show a higher need for intra aortic balloon pump post-PCI when compared with distal LAD culprit lesions. In right coronary artery and LC related infarcts, proximal versus distal culprit lesions show no differences in the need for intra aortic balloon pump post-PCI. In LAD related infarcts, proximal culprit lesions are associated with a lower incidence of myocardial blush grade 2/3 post-PCI when compared with distal culprit lesions. In right coronary artery and LC related infarcts no differences are seen in PCI success or incidence of myocardial blush grade 2/3 in proximal versus distal

culprit lesions. The primary endpoints all cause mortality at 30 days and 3 years are presented in table 3. Only in LAD related infarcts proximal culprit lesions have a higher short and long-term mortality when compared with distal culprit lesions.

The relative risk of 3-year mortality for proximal LAD versus distal LAD culprit lesions, adjusted for age, gender, diabetes mellitus, ischemic time and multi vessel disease was 4.04 (95% CI 1.95 – 8.38). No difference is seen in adjusted 3-year mortality between distal LAD culprit lesions and non-LAD culprit lesions (p=0.145). The secondary endpoints enzymatic infarct size and residual LVef are shown in table 4. In LAD related infarcts proximal culprit lesions have a larger enzymatic infarct size and lower residual LVef when compared with distal culprit lesions. In right coronary artery and LC related infarcts proximal culprit lesions have comparable infarct size and residual LVef when compared with distal culprit lesions.

Table 3. Primary endpoint; all cause mortality.

Infarct Coronary Artery Occlusion site	Right proximal (n=316)	Right distal (n=197)	p	Left Circumflex proximal (n=79)	Left Circumflex distal (n=113)	p	Left Anterior Descending proximal (n=398)	Left Anterior Descending distal (n=365)	p
30-day mortality	6(2%)	2(1%)	0.430	3(4%)	3(3%)	0.627	21(5%)	2(1%)	0.002
3-year mortality	13(4%)	12(6%)	0.363	5(6%)	7(6%)	0.895	39(10%)	9(3%)	<0.0001

Table 4. Secondary endpoints; enzymatic infarct size and residual left ventricular function.

Infarct Coronary Artery Occlusion site	Right proximal (n=316)	Right distal (n=197)	*p*	Left Circumflex proximal (n=79)	Left Circumflex distal (n=113)	*p*	Left Anterior Descending proximal (n=398)	Left Anterior Descending distal (n=365)	*p*
Enzymatic infarct size	1210±1053	1226±880	*0.311*	1849±1727	1251±860	*0.079*	2200±1580	1660±1476	*<0.0001*
Left Ventricular ejection fraction(%)	50±8	50±7	*0.973*	47±9	48±8	*0.360*	37±11	42±11	*<0.0001*

Enzymatic infarct size is defined as cumulative Lactate Dehydrogenase release (U/l) up to 36 hours post-AMI

Discussion

This study shows that in patients with acute ST segment elevation myocardial infarction treated with primary PCI early after the onset of symptoms, proximal LAD culprit lesions are associated with a lower residual LVef and higher short and long-term mortality when compared with distal LAD culprit lesions. In right coronary artery and LC related infarcts short and long-term mortality and residual LVef between proximal and distal culprit lesions are comparable. No difference is seen in long-term mortality between distal LAD and non-LAD related infarcts. In right coronary artery and LC related infarcts lesion location did not influence PCI success. In our mortality analyses for LAD related infarcts we adjusted for variables assumed to have an affect on the outcome. In the pre-reperfusion era and in patients treated with thrombolysis as reperfusion therapy involvement of the right ventricle in right coronary artery related infarcts is associated with worse prognosis. Our data show that in patients with right coronary artery related infarcts, treated with primary PCI, proximal occlusions have similar prognosis when compared with distal occlusions. The better prognosis of proximal right coronary artery culprit lesions in our study is due to higher reperfusion rates achieved with primary PCI. Previous studies showed after successful restoration of reperfusion a prompt recovery of right ventricular systolic function[19,20]. Many studies have shown that irrespective of the given reperfusion therapy, LAD related infarcts have worse clinical outcome compared to non-LAD related infarcts. Our study shows that when looking at survival, hemodynamic and angiographic outcome measures in relation to occlusion site, proximal and distal LAD culprit lesions show a different outcome. Proximal LAD culprit lesions have worse pre- and post interventional hemodynamic conditions, represented as higher Killip class at presentation and more frequent need for intra aortic balloon pump. This is probably associated with the larger area of myocardium at risk in proximal LAD related infarcts. We also see a lower myocardial blush grade in proximal LAD culprit lesions.

Whether this is also related to the larger infarct size remains speculative. It could be that this is due to more edema, higher filling pressures and downstream

resistance in proximal LAD related infarcts[13]. Even after adjusting for these factors, proximal LAD culprit lesions have higher long-term mortality and lower residual LVef when compared with distal LAD culprit lesions and non-LAD culprit lesions. In our analyses is shown that mainly proximal LAD related infarcts are the ones at high risk. After successful early reperfusion with PCI, distal LAD related infarcts have equal survival rates as non-LAD related infarcts. A limitation is that LVef and enzymatic infarct size was not available in all patients. Since their benefits have only been recently proven, additional administration of IIb-IIIa inhibitors have only been applied in 5% of our population[21]. Furthermore no distal protection devices have been used in this series of patients.

Conclusion

Our analysis show that even in patients with acute MI treated with early PCI the proximal LAD related infarcts have the worst 3-year survival and lowest residual LVef when compared with distal LAD related infarcts and non-LAD related infarcts. In right coronary artery and LC related infarcts no difference is seen in 3-year survival and residual LVef in proximal versus distal culprit lesions.

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Summary and Conclusions

In this thesis we address the impact of various clinical and angiographic aspects on clinical outcome in a setting where patients presenting with acute myocardial infarction are systematically treated with early primary PCI.

In chapter 1 we give as introduction a chronological overview of the acute MI treatment in the past decades followed by an overview of this thesis.

In chapter 2 we analysed whether clinical episodes of myocardial ischaemia, defined as intermittent episodes of angina in the hours or days before acute myocardial infarction (MI), are of clinical relevance with regard to myocardial protection. We found that preinfarction angina is present in about 50% of patients presenting with acute MI. These patients seem to wait longer before seeking medical attention in the setting of an acute MI. On the other hand, preinfarction angina < 24 hours has a protective effect on infarct size due to a higher incidence of collateral flow to the infarct related artery and due to ischaemic preconditioning.

In chapter 3 we tried to identify an early and widely available marker for risk stratification. We showed that although Lactate DeHydrogenase (LDH) release after acute MI continuous up to 96 hours, the cumulative release measured at 36 hours post MI is a good and reliable early biomarker for predicting residual left ventricular function and 1-year mortality.

In chapter 4 we showed that in the first hours of infarction angiographically detectable collateral flow to the epicardial infarct related coronary artery (Rentrop grade 2 or 3) is present in about 10% of the patients. These early collaterals have a protective effect on infarct size, defined as smaller enzymatic infarct and better myocardial blush, and a protective effect on pre- and post-intervention hemodynamic conditions, defined as lower incidence of Killip class ≥ 2 at presentation and decreased use of intra aortic balloon pumping post-PCI. This protective effect is especially present in LAD related infarcts.

In chapter 5 we showed that the worse residual left ventricular function and the worse prognosis of LAD related infarcts is not only related to the larger infarct size. The enzymatic infarct size for LAD related infarcts is larger, though for every 1000 U/l cumulative LDH release, LAD related infarcts have a 4.7 % decrease in LVef as compared to 2.4 % decrease in LVef for non-LAD related infarcts.

In chapter 6 we evaluated whether the risk stratification based on occlusion site. In acute MI patients treated with thrombolytic therapy, proximal occlusions have a worse prognosis when compared to distal occlusions, irrespective the coronary artery. Nowadays primary PCI is the treatment of choice in acute MI. We compared short and long term mortality in proximal versus distal coronary occlusions in acute MI patients treated with primary PCI. We found that no difference was found in RCA and CX related infarcts, but occlusion of the proximal LAD was associated with a nearly 4 times higher mortality as compared to distal LAD related infarcts.

Final comments.

The past two decades the treatment of choice for acute MI has evolved rapidly, resulting in better survival. Nowadays primary PCI is the treatment of choice. Despite this highly efficient reperfusion therapy, anterior located infarcts, especially those related to a proximal occlusion of the LAD, remain the group with the worse prognosis. The future challenge is focused on the question how to decrease myocardial damage further in the early reperfused patients, to improve prognosis, especially in this high risk group of patients, where the greatest benefit is to be gained. In this thesis, we show that intermitted episodes of myocardial ischaemia in the hours and days preceding the acute MI, defined as pre-infarction angina, protect the jeopardized myocardium by delaying necrosis. This benefit seems partly due to increased collateral flow and partly due to preconditioning of the jeopardized myocardium. Furthermore collateral flow indeed protects the jeopardized myocardium in the setting of acute MI. Preconditioning is not a mechanism which can be used in the clinical setting of acute MI. Recent studies show that post-conditioning is also a possible potent mechanism for protecting the jeopardized non-necrotic myocardium. A significant part of the final infarct size is still vital at the time of reperfusion. This part is lost due to the so called lethal reperfusion-induced injury, with apoptotic cell death as an important contributor[1-3]. Postconditioning is a possible tool to protect this part of the jeopardized myocardium, by stimulating the same survival protein kinase pathways responsible for the cardio-protective effect in preconditioning[4]. Postconditioning

can be initiated by mechanical and farmacological interventions at the time of reperfusion[4,5]. Further clinical research is necessary whether this potential powerful tool is indeed of important clinical relevance and easy to incorporate in daily clinical practice. Another future challenge is to give the most optimal reperfusion therapy to a much larger group of acute MI patients. According to the European Heart Survey only 57% of the acute MI patients nowadays receive reperfusion therapy and only 21% primary PCI[6]. According to the data of the European Heart Survey, the availability of PCI-facilities is an important factor for receiving reperfusion therapy. Strategies to increase the availability of PCI-facilities for all patients could increase the amount of acute MI patients receiving primary PCI as reperfusion therapy. These strategies could be a well organised pre-hospital acute MI triage and the availability of at least one PCI-facility in every ambulance region, which is not yet the case in our country.

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Nederlandse Samenvatting

In dit proefschrift worden diverse klinische en angiografische aspecten belicht die invloed hebben op de prognose en het klinische beloop van patienten, die zich presenteren met een acuut myocardinfarct, en systematisch worden behandeld met vroege primaire PCI.

In hoofdstuk 1 wordt als introductie een chronologisch overzicht gegeven van de behandeling van het acute myocardinfarct in de afgelopen decennia, gevolgd door een overzicht van dit proefschrift.

In hoofdstuk 2 hebben we onderzocht of klinische episodes van myocard ischaemie, gedefinieerd als episodes van passagere angina pectoris, in de uren en dagen voorafgaand aan het acute myocardinfarct, myocard necrose vertraagt. We vonden dat pre-infarct angina pectoris in de helft van de patiënten met een acuut myocardinfarct voorkomt. Deze patiënten wachten langer voordat zij medische hulp inroepen bij klachten van een acuut myocardinfarct. Pre-infarct angina pectoris in de 24 uur voorafgaand aan het acute myocardinfarct werkt beschermend door een betere collateraal vorming naar het bedreigde myocard en via ischaemische preconditionering van het myocard.

In hoofdstuk 3 hebben we geprobeerd een eenvoudige marker te identificeren die kort na het myocardinfarct een risico stratificatie mogelijk maakt. We laten zien dat hoewel Lactate DeHydrogenase (LDH) tot 96 uur na het myocardinfarct vrijkomt in de bloedbaan, de cumulatieve afgifte op 36 uur na het myocardinfarct, een goede en betrouwbare biomarker is voor het voorspellen van de linker ventrikel restfunctie en 1-jaars mortaliteit.

In hoofdstuk 4 laten we zien dat in de eerste uren van een acuut myocardinfarct bij ongeveer 10% van de patiënten angiografisch collaterale flow naar het epicardiale infarct gerelateerd vat (Rentrop graad 2 of 3) zijn te detecteren. Deze vroege collateralen hebben een beschermende werking op het bedreigde myocard, gedefinieerd als kleiner enzymatisch infarct en betere myocardiale blush. Ook hebben ze een beschermend effect op de hemodynamische toestand van de patiënt, zowel voor als na de coronair interventie. Dit uit zich in een lagere incidentie van Killip klasse ≥ 2 bij presentatie en een lagere noodzaak voor het geven van een intra-

aortale ballonpomp. Dit beschermende effect van de vroege collateralen is met name aanwezig in de LAD gerelateerde infarcten.

In hoofdstuk 5 tonen we dat de slechtere linker ventrikel restfunctie en de slechtere prognose van LAD gerelateerd infarcten vergeleken met andere infarct locaties, niet alleen gerelateerd is aan het groter gebied van geinfarceerd myocard. Het enzymatische infarct is voor LAD gerelateerde infarcten gemiddeld gezien inderdaad groter. Indien we echter kijken naar de relatie tussen linker ventrikel ejectiefractie (LVef) en enzymatische infarct grootte, blijkt dat elke 1000 U/l cumulatief LDH verlies, leidt tot een 4,7% afname van LVef in LAD gerelateerde infarcten en een 2,4% afname van LVef in niet LAD gerelateerde infarcten..

In hoofdstuk 6 hebben we onderzocht of de risico stratificatie gebaseerd op occlusieplaats, zoals gedefinieerd bij infarct patiënten behandeld met thrombolyse, nog steeds actueel is bij behandeling met primaire PCI. Bij patiënten met een acuut myocardinfarct, behandeld met thromolyse, hebben proximale occlusies een slechtere prognose dan distale occlusies, ongeacht welke coronair arterie. Tegenwoordig is primaire PCI de eerste keus behandeling van het acute myocardinfarct. Wij vonden dat bij patiënten met een acuut myocardinfarct, behandeld met een primaire PCI, proximale en distale occlusies in RCA en CX en distale LAD gerelateerde infarcten een vergelijkbare korte en lange termijn mortaliteit tonen. Terwijl de korte en lange termijn mortaliteit voor proximale LAD occlusies aanzienlijk slechter is vergeleken met alle andere locaties.

Slotopmerkingen

De laatste twee decennia heeft de behandeling van het acute myocardinfarct zich snel ontwikkeld, resulterend in een betere overleving. Tegenwoordig is primaire PCI de eerste keus behandeling. Ondanks deze effectieve reperfusie therapie blijven voorwand infarcten, met name die gerelateerd aan proximale LAD occlusies, de groep met de slechtste prognose.

De uitdaging voor de toekomst is gericht op de vraag hoe de myocardschade bij de vroeg gereperfundeerde patiënt verder te verlagen en zo de prognose

verder te verbeteren. Wij laten zien dat pre-infarct angina pectoris in de 24 uur voorafgaand aan het acute myocardinfarct myocardschade vertraagt. Dit voordeel wordt veroorzaakt door toegenomen collaterale flow en door ischaemische preconditionering van het bedreigde myocard. Zoals in dit proefschrift aangetoond beschermen vroege collateralen inderdaad het bedreigde myocard. Ischaemische preconditionering van het myocard is niet klinisch toepasbaar bij patiënten met een acuut myocardinfarct. Recente studies tonen dat postconditionering ook een mogelijk potent beschermingsmechanisme is voor het bedreigde nog vitale myocard.

Een significant deel van het uiteindelijk geinfarceerde myocard is op het moment van de reperfusie nog vitaal. Dit deel gaat na de reperfusie alsnog verloren als gevolg van de door reperfusie geïnduceerde letale beschadiging, waarvan apoptotische celdood een belangrijke bijdrage is. Het potentiële beschermingsmechanisme van postconditionering op het bedreigde myocard ontstaat door stimulatie van dezelfde "survival protein kinase pathways" die verantwoordelijk zijn voor het cardio-protectieve effect bij preconditionering. Postconditionering van het myocard kan gerealiseerd worden door zowel mechanische als farmacologische interventies op het moment van reperfusie. Verder klinisch onderzoek is nodig om duidelijk te krijgen of deze potentieel potente beschermingsmechanismen inderdaad van klinische relevantie zijn en of dit inderdaad gemakkelijk in de klinische praktijk is in te passen. Een andere belangrijke toekomstige uitdaging is de vraag hoe primaire PCI, als behandeling voor het acute myocardinfarct, voor een zo groot mogelijke groep patiënten te realiseren is. Volgens de European Heart Survey krijgt slechts 57% van de patiënten met een acuut myocardinfarct reperfusie therapie, waarvan slechts 21% primaire PCI. Uit deze survey blijkt ook dat de beschikbaarheid van PCI-faciliteiten een belangrijke factor is voor het krijgen van reperfusie therapie.

Strategieën die de beschikbaarheid van PCI faciliteiten vergroot, kunnen leiden tot een forse toename van het aantal patiënten met een acuut myocardinfarct die primaire PCI als reperfusie therapie krijgen. Deze strategieën kunnen bestaan uit een brede, goed georganiseerde pre-hospitale triage en de beschikbaarheid van tenminste één PCI-faciliteit in elke ambulance regio,wat op dit moment nog niet het geval is in ons land.

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Curriculum Vitae

Peter Elsman werd op 10 januari 1965 te Portugaal geboren. Hij behaalde in 1984 zijn eindexamen Atheneum aan de christelijke scholengemeenschap Jan Arentsz te Alkmaar. Hetzelfde jaar begon hij met de studie geneeskunde aan de Vrije Universiteit te Amsterdam. In 1990 behaalde hij zijn doctoraalexamen en in 1993 zijn artsexamen. Aansluitend deed hij zijn eerste cardiologie ervaring op als arts-assistent in het Zuider ziekenhuis te Rotterdam en in 1994 als arts-assistent op de afdeling cardiologie in het Academisch Ziekenhuis Maastricht. In 1995 startte hij zijn werkzaamheden als arts-assistent op de afdeling cardiologie van de Isala klinieken in Zwolle. In 1996 startte zijn opleiding tot cardioloog die in 2002 werd afgerond (cardiologie opleiding locatie Weezenlanden; opleider dr. J.C.A. Hoorntje, interne vooropleiding locatie Sophia; opleider dr. M. van Marwijk Kooij). Gedurende deze periode werd de basis gelegd voor dit proefschrift. Van 2003 tot 2004 was hij als staflid interventiecardioloog werkzaam in het Universitair Medisch Centrum St. Radboud te Nijmegen. Vanaf 2004 tot heden is hij werkzaam als interventiecardioloog in het Universitair Medisch Centrum Utrecht. Vanaf januari 2006 maakt hij tevens deel uit van de maatschap cardiologie van het Jeroen Bosch Ziekenhuis, locatie BMC, te ‘s Hertogenbosch. Hij is getrouwd met Natasja Hehanussa en heeft 3 zonen, Thomas (1998), Stefan (2000) en Martijn (2003).

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MSD BV
Novartis Pharma BV
Bristol-Myers Squibb BV
Boehringer Ingelheim BV
Braun Medical BV
TOP Medical BV
AstraZeneca BV
Cordis BV
Abbott Vascular BV
Pfizer BV
Sanofi Aventis BV
Eli Lilly BV
Dynamic Medical BV